Nested Case-Control Study of External Ionizing Radiation Dose and Mortality From Dementia Within a Pooled Cohort of Female Nuclear Weapons Workers

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Background *A prior investigation of this cohort of female nuclear workers found increased deaths from mental disorders, including dementia. The present study estimates the effect of workplace exposures to ionizing radiations and other hazards on mortality from dementia.*
Methods *A nested case-control study within a pooled cohort of 67,976 female nuclear workers compared 91 cases of death from dementia with 910 controls. Adjusted odds ratios (ORs) were employed to estimate the effects of maximum annual and total lifetime radiation doses on the occurrence of dementia in 168 monitored workers.*
Results *Both maximum annual (OR = 2.11, 95% confidence interval (CI) = 0.98, 4.40) and total lifetime radiation doses (OR = 2.09, 95% CI = 1.02, 4.29) were associated with death from dementia. Significant dose-response trends were present for both exposures.*
Conclusions *Occupational exposure to ionizing radiation (IR) may be associated with increased risk of death from dementia in female workers. Since these findings are based on a small number of cases, replication with a larger case sample should be pursued.* Am. J. Ind. Med. 44:351–358, 2003. *© 2003 Wiley-Liss, Inc.*

KEY WORDS: dementia; occupational exposure; radiation effects; epidemiology; case-control studies

INTRODUCTION

In a study of female workers from 12 US nuclear weapons plants, Wilkinson et al. [2000] unexpectedly found increased mortality from mental disorders. The most common diagnosis was dementia, which accounted for 91 of the 166 deaths from mental disorders. The present investigation was undertaken to estimate the effect of workplace exposures to ionizing radiation (IR) and other hazards on mortality from dementia.

Exposure to heavy doses of IR can lead to cognitive impairment in children [Ron et al., 1982; Rowland et al., 1984] and in adults receiving radiotherapy to the head [Scott et al., 1998; Pierga et al., 1999; Vigliani et al., 1999; Meyers et al., 2000]. To date, however, only one study other than Wilkinson et al. [2000] suggests an increased risk of death

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from dementia in adults receiving low-level occupational exposure to IR. Schulte et al. [1996] reported that, compared with workers in other occupations, an increased proportion of white female radiologic technicians experienced death from Alzheimer disease (AD) (proportionate mortality ratio = 241; 95% confidence interval (CI) = 132, 405).

Wilkinson et al. [2000] constructed a cohort that combined female workers from 12 US nuclear weapons facilities. This pooled population consists of 67,976 women who were hired at any of these 12 plants[1] between 1943 or start of facility operations and 1979, and followed from hire date through 1994. Death certificates were available for 13,671 workers who were known to have expired before January 1, 1995. The purpose of the present study is to estimate the effects of exposure to IR on the occurrence of death from dementia in female nuclear workers.

METHODS

Study Sample

A nested case-control study was conducted within the cohort described above. Cohort members were employed for at least 1 day in one of the aforementioned nuclear weapons facilities and were hired between 1943 and 1979. Vital status was determined for the pooled cohort by matching individuals not already known to be deceased with social security administration master death tapes using a matching algorithm developed by the epidemiology research institute. The vital status of individuals who were identified as deceased was confirmed by obtaining death certificates from state departments of vital statistics. Death certificates were then coded for underlying cause of death by a qualified nosologist. The 91 cases are women who died prior to January 1, 1995, and whose death certificates listed dementia as the underlying cause of death. The present analysis is based on data for 1,001 individuals, 91 cases, and 910 controls, who were selected randomly from the pool of workers with a ratio to cases of 10:1.

Selection of controls

Since all 91 cases were born before 1930, the pool of potential controls was limited to workers meeting that requirement. Since there were no cases from Fernald, Linde, or Mound, those three sites were eliminated from the pool of eligible controls.[2] Workers dying before 1972, the 1st year in which a case died, were also excluded, leaving a pool of 41,729 potential controls. This group was sorted randomly, using the SPSS UNIFORM procedure [Kinnear and Grey, 2000]. For each case, the first 10 workers from the randomized list that were still alive in her year of death were selected. Of the controls, 154 had been monitored for external radiation. These workers served as controls for the 14 monitored cases of death from dementia in analyses of the effects of radiation exposure.

Identification of Cases

The outcome variable, death from dementia, was defined as present when the death certificate listed the underlying cause of death as either Senile Dementia (ICD-8: 290.0) or Pre-Senile Dementia (290.1). Causes of death were coded according to the 8th revision of the International Classification of Diseases (World Health Organization, 1965), which was in use through 1978. The codes for Senile Dementia (290.0) and Pre-senile Dementia (290.1), including Alzheimer disease, are unchanged in the 9th revision.

Monitoring Status

Because only a portion of the study population had a health physics record, we recorded whether a worker had been monitored for external radiation. One hundred sixty-eight (14 cases and 154 controls) of the 1,001 study workers had at least one film badge or thermoluminescent detector (TLD) reading recorded in a health physics record. Furthermore, because it is not known if unbadged workers experienced any workplace exposure to radiation, estimates of the effects of radiation doses were limited to the monitored subpopulation of cases and controls.

Exposure Measures

Maximum annual radiation dose

The highest annual radiation dose in millisievert was recorded for those cases that were monitored for external radiation and for monitored controls. Maximum annual dose is categorized as follows: 0.0–4.9 mSv (baseline), 5.0–9.9 mSv, 10.0–24.9 mSv, and 25.0–49.9 mSv.

Total lifetime radiation dose

The total lifetime dose in millisievert was recorded for those workers who wore film badges or TLDs. The categories of cumulative lifetime dose are: 0.0–9.9 mSv (baseline), 10.0–24.9 mSv, 25.0–49.9 mSv, and $\geq$50 mSv.

Selected sociodemographic variables and potential confounders

The following variables were recorded and evaluated as potential effect modifiers or confounders: race/ethnicity, age

[1] The facilities studied were: Oak Ridge, TN (K25, X10, Y12); Los Alamos National Laboratory and Zia Co., NM; Rocky Flats, CO; Hanford, WA; Mound, OH; Savannah River, SC; Fernald, OH; Linde, NY; and Pantex, TX.

[2] Workers at these three sites comprised only 4% of the total cohort (n = 2,709).

at hire, number of years worked, age at risk,[3] years of follow-up, age first monitored for external radiation, number of years monitored, and facility. Continuous variables were divided into tertiles for analyses involving the entire study sample and dichotomized at the median in the monitored sub-sample (n = 168). When facility of employment was considered, either in stratified or multivariate analyses, it was treated as a categorical variable.

Statistical Analysis

Stratified analysis

The associations of monitoring status, maximum annual dose, and total lifetime dose with death from dementia were stratified by levels of the potential confounders listed above. Mantel–Haenszel (M–H) tests of the heterogeneity of ORs across strata were performed. Marked differences in ORs between strata were interpreted as evidence of effect modification. Large discrepancies between the combined M–H estimate of the OR and the crude, unstratified estimate were taken as evidence of confounding [Kleinbaum et al., 1982]. The covariates affecting each association are identified below.

Multivariate analysis

The small number of cases dictated the use of simple models to assess main effects of exposures and selected covariates. Hierarchical models including interaction terms produced extremely large and imprecise point estimates that were uninterpretable. (Data not shown.)

Monitoring status, highest annual radiation dose, and total lifetime dose were analyzed separately in relation to death from dementia. An exact logistic regression model [LogXact for Windows, 1996] estimated ORs adjusted for those covariates identified as confounders or effect modifiers in the stratified analysis. For all analyses, highest annual dose and total lifetime dose were categorized as described above. The ORs for the various exposure levels were also tested for dose trends [Clayton and Hills, 1993]. All statistical analyses utilized either LogXact for Windows [1996] or STATA, Version 7 [2002]. All point estimates and CIs are based on exact inference, except where otherwise noted.

RESULTS

Case-Control Comparisons

Selected sociodemographic and work-related characteristics are presented in Table I. The distribution of cases and controls by tertiles of age at hire, years worked, age at risk,

[3] Censoring occurred at death or the end of follow-up, 12/31/1994.

TABLE I. Selected Sociodemographic* and Work-Related Characteristics of Cases and Controls in a Pooled Cohort of Female Nuclear Weapons Workers (n = 1,001)

	Cases (n = 91)		Controls (n = 910)	
Characteristic	**n**	**(%)**	**n**	**(%)**
Race/ethnicity[a]				
White	84	(92.3)	855	(94.0)
Black	7	(7.7)	55	(6.0)
Age at hire (years)				
16–21	8	(8.8)	316	(34.7)
22–29	19	(20.9)	322	(35.4)
30–59	64	(70.3)	272	(29.9)
Years worked				
<1	26	(28.6)	345	(37.9)
1	20	(22.0)	222	(24.4)
2–49	45	(49.5)	343	(37.7)
Age at risk[b] (years)				
59–69	19	(20.9)	285	(31.3)
70–75	18	(19.8)	356	(39.1)
76–106	54	(59.3)	269	(29.6)
Years of follow-up				
15–46	65	(71.4)	237	(26.0)
47–49	24	(26.4)	377	(41.4)
50–51	2	(2.2)	296	(32.5)
Monitoring status				
Monitored	14	(15.4)	154	(16.9)
Unmonitored	77	(84.6)	756	(83.1)

*Information regarding education level was not available.
[a]Race/ethnicity was categorized only as White or Black. Workers for whom race/ethnicity was unknown were coded as White.
[b]Age at death or end of follow-up (12/31/1994).

and years of follow-up are shown. Over 70% of cases were older than 29 years of age when hired, compared with 30% of controls. Number of years worked was comparable for cases and controls. Over half of the sample worked for 1 year or less. More than half the cases were over age 75 at death. Over 90% of controls, (not shown in table), were still alive at the end of follow-up on 12/31/1994. Only 30% of them had reached age 76 by that date. The follow-up period runs from year hired to the end of study or the year in which a worker died. This period is slightly longer, on average, for controls than for cases.

Possible differences in radiation dose effect estimates between cases and controls for age at hire, age at risk, and years of follow-up were explored in the stratified analysis.

Monitored Sub-Sample

Fourteen (15.4%) of 91 cases and 154 (16.9%) of 910 controls wore radiation monitors. Table II presents data for

TABLE II. Selected Sociodemographic* and Work-Related Characteristics of a Pooled Cohort of Female Nuclear Weapons Workers Who Were Monitored for External Radiation (n = 168)

	Cases (n = 14)		Controls (n = 154)	
Characteristic	**n**	**(%)**	**n**	**(%)**
Race/ethnicity[a]				
White	14	(100.0)	149	(96.8)
Black	0		5	(3.2)
Age at hire (years)				
17–31	3	(21.4)	79	(51.3)
32–55	11	(78.6)	75	(48.7)
Years worked				
<1–14	5	(35.7)	79	(51.3)
15–49	9	(64.3)	75	(48.7)
Age at risk[b] (years)				
65–71	5	(35.7)	85	(55.2)
72–91	9	(64.3)	69	(44.8)
Years of follow-up				
15–43	6	(42.9)	75	(48.7)
44–51	8	(57.1)	79	(51.3)
Age first monitored				
19–36	7	(50.0)	78	(50.6)
37–63	7	(50.0)	76	(49.4)
Years monitored				
<1–4	6	(42.9)	78	(50.6)
5–40	8	(57.1)	76	(49.4)

*Information regarding education level was not available.
[a]Race/ethnicity was categorized only as White or Black. Workers for whom race/ethnicity was unknown were coded as White.
[b]Age at death or end of follow-up (12/31/1994).

the sub-sample of monitored workers, including two additional variables, age first monitored, and years monitored. The proportions of cases and controls falling below and at or above the median for each variable are shown. Cases were somewhat older than controls when hired. The higher values in this subgroup for years worked indicate that badged workers were on average employed longer than were unbadged workers. The difference in age at end of study or at death is consistent with the findings for the entire study population. Age first monitored is comparable in cases and controls, but cases tended to be monitored for a longer period.

Radiation Exposure Data

As noted earlier, 14 of 91 demented cases and 154 of 910 controls were monitored for radiation from external sources. Table III shows that monitored cases came from only four sites: Hanford (n = 9), Los Alamos (n = 1), Rocky Flats (n = 1), and X10 (n = 3). While some controls at each site were badged, the proportions monitored varied markedly across sites, from 4.1% (n = 17) at Y12 to 85% (n = 34) at X10. In general, the proportions of monitored workers by site were comparable for cases and controls.

Bivariate Analysis

Potential covariates

The associations between seven potential covariates and death from dementia are presented in Table IV. Each variable, except for race/ethnicity, was treated as a continuous measure in order to generate crude ORs for this analysis. Most

TABLE III. Proportion of Cases and Controls by Site Who Were Monitored for External Radiation in a Pooled Cohort of Female Nuclear Weapons Workers (n = 1,001)

	Cases (n = 91)					Controls (n = 910)				
	Monitored		Unmonitored			Monitored		Unmonitored		
Site[a]	**n**	**(%)**	**n**	**(%)**	**Total**	**n**	**(%)**	**n**	**(%)**	**Total**
Hanford	9	(75.0)	3	(25.0)	12	67	(54.5)	56	(45.5)	123
K25	0	—	14	(100.0)	14	11	(6.4)	162	(93.6)	173
Los Alamos	1	(10.0)	9	(90.0)	10	12	(14.0)	74	(86.0)	86
Pantex	0	—	1	(100.0)	1	1	(14.3)	6	(85.7)	7
Rocky Flats	1	(50.0)	1	(50.0)	2	4	(50.0)	4	(50.0)	8
Sav. River	0	—	1	(100.0)	1	5	(45.5)	6	(54.5)	11
X10	3	(75.0)	1	(25.0)	4	34	(85.0)	6	(15.0)	40
Y12	0	—	42	(100.0)	42	17	(4.1)	396	(95.9)	413
Zia	0	—	5	(100.0)	5	3	(6.1)	46	(93.9)	49
Total	14	(15.4)	77	(84.6)	91	154	(16.9)	756	(83.1)	910

[a]There were no cases of death from dementia at Fernald, Linde, or Mound. Therefore, these three sites were eliminated from the population giving rise to the cases.

TABLE IV. Crude ORs and 95% CIs for Death From Dementia and Selected Sociodemographic and Work-Related Characteristics in a Pooled Cohort of Female Nuclear Weapons Workers

	Full sample (n = 1,001)		Monitored workers (n = 168)	
Characteristic	Crude OR	95% CI	Crude OR	95% CI
Race/ethnicity	1.30[a]	0.48, 2.98	—[b]	—
Age at hire	1.09	1.07, 1.12	1.04	0.98, 1.10
Years worked	1.00	0.98, 1.03	0.99	0.95, 1.03
Age at risk[c]	1.07	1.04, 1.11	1.11	1.02, 1.20
Years of follow-up	0.93	0.90, 0.95	1.02	0.95, 1.08
Years monitored	—	—	1.01	0.96, 1.06
Age first monitored	—	—	1.01	0.96, 1.06

OR, odds ratio; CI, confidence interval.
[a]OR for Black workers compared with White workers.
[b]All monitored cases were White.
[c]Age at death or end of follow-up (12/31/1994).

point estimates are close to unity. For the full sample, age at hire and age at risk are positively associated with death from dementia, while years of follow-up is negatively associated with this outcome. In the monitored sub-sample, age at risk continues to show a positive association with death from dementia.

Monitoring status

As shown in Table V, analysis of the association between monitoring status and death from dementia for the full study sample of 1,001 produces a crude OR of 0.89 (95% CI = 0.45, 1.64).

Radiation exposure

Table VI shows the relative proportions of monitored cases and controls exposed to various levels of radiation (in millisievert) for both maximum annual dose and total lifetime dose. Over 28% of cases (n = 4), but only 9% of controls (n = 14), had maximum annual exposures of 5 mSv or higher. For total lifetime radiation dose, 42% of cases (n = 6) had exposures exceeding 10 mSv, while 14% of controls (n = 22) experienced this level of exposure.

In order to test for dose-response trends, Mantel–Haenszel analyses [STATA, Version 7, 2002] were performed. Crude ORs for maximum annual radiation doses range from 2.00 to 14.00. The point estimates for total lifetime dose also increase at higher exposure levels, from 3.54 to 6.60. The 95% CIs for these estimates are very wide and all include unity except for total lifetime doses of ≥50 mSv (OR = 6.60, 95% CI = 1.06, 41.10). There is a statistically significant trend of increasing effects as dose increases for both maximum annual dose ($P = 0.006$) and total lifetime dose ($P = 0.005$). When the higher dose categories are compared with the lowest dose category, ORs of 2.23 (95% CI = 1.06, 4.45) for maximum annual doses and 1.99 (95% CI = 1.10, 3.46) for total lifetime doses are observed.

Multivariate Analysis

Monitoring status (n = 1,001). The strength of this association was assessed by unconditional logistic regression adjusting for the covariates identified in the stratified analysis: age at hire, age at risk, and years of follow-up. The resultant OR of 0.33 (95% CI =0.17, 0.64),[4] shown in Table V, indicates a significant protective effect for women badged for the detection of IR.

Radiation exposure (n = 168)

Only 14 monitored workers were identified as having died from dementia. Table VI shows the association of maximum annual radiation dose with death from dementia, adjusting for age at risk, and other identified effect modifiers (years of follow-up and age first monitored). A M–H analysis of these data yields ORs increasing from 2.44 to 7.60 at higher exposures. Although the CIs for these point estimates are quite broad, the dose-response trend is statistically significant ($P = 0.022$). An overall analysis, comparing the higher levels of exposure with the baseline category (0.0–4.9 mSv) produces an OR of 2.11 (95% CI = 0.98, 4.40).

Lifetime radiation dose was categorized as shown in Table VI. The M–H analysis of these data again shows a dose-response trend.[5] Although the CIs are very wide, the trend test yields a probability (that this finding is due to chance) of 0.003. When the overall association of this exposure with death from dementia is adjusted for age at risk and the effect modifiers identified in the stratified analysis (years of follow-up, age first monitored, and number of years monitored), OR = 2.09 (95% CI = 1.02, 4.29).

DISCUSSION

This multi-site nested case-control study of a pooled cohort totaling 67,976 female nuclear workers was undertaken to estimate the effect of radiation dose on death from dementia. Present findings of an increased risk of developing dementia as a result of exposure to external IR are consistent with earlier studies on the cognitive sequelae of radiotherapy

4 These results are based on asymptotic inference as the number of variables in the model precludes an exact calculation.
5 No OR estimate is available for doses of 25.0–49.9 mSv, since only a single case fell in this category.

TABLE V. Crude and Adjusted ORs and 95% CIs for Death From Dementia and Monitoring Status in a Pooled Cohort of Female Nuclear Weapons Workers (n = 1,001)

Monitoring Status	Cases	Controls	Crude OR	95% CI	Adjusted OR[a]	95% CI
Unmonitored	77	756	1.00		1.00	
Monitored	14	154	0.89	0.45, 1.64	0.33	0.17, 0.64

[a]Adjusted for age at hire, age at risk, and years of follow-up.

to the head and neck [Scott et al., 1998; Pierga et al., 1999; Vigliani et al., 1999; Meyers et al., 2000], but not with data on the prevalence of AD in ageing atomic bomb survivors [Yamada et al., 1999]. However, individuals in the studies cited received much higher doses of radiation over a relatively brief time period, whereas women in the present study typically received low doses over a much longer time period, over 20 years in some cases. The results here are consistent with Russian reports of cognitive impairments following occupational radiation exposures in clean-up workers following the accident at Chernobyl [Zhavoronkova et al., 1997; Ponomarenko et al., 1999].

This investigation found evidence of a lower risk of death from dementia in women monitored for external radiation (OR = 0.33, 95% CI = 0.17, 0.64). This finding may represent a ''healthy worker effect,'' i.e., employed persons tend to have better overall health and survival than an unselected general population (e.g., Baillargeon et al., 1998).

Not reported here, due to space limitations, are the results of an investigation of the risk of death from dementia in cohort members having occupational exposure to neurotoxic chemicals. Exposure was estimated from a worker's job category (e.g., machinist versus clerical worker). No association was found between death from dementia and this proxy measure of chemical exposure.[6]

Death from dementia was defined in this study by death certificate data, which often have proved subject to classification error. Ganguli and Rodriguez [1999] found that two-thirds of decedents clinically diagnosed as demented did not have that disorder listed on their death certificates. In the present study, demented individuals who died of another cause were not counted as cases. Also excluded were decedents for whom dementia may have been listed as a ''contributory'' rather than the ''underlying'' cause of death.

Reference dose categories used in this study were defined as <5 mSv for maximum annual dose and <10 mSv for total lifetime dose. These limits are consistent with those used in other investigations of occupational radiation exposure [Baillargeon et al., 1998; Ritz et al., 1999; Sont et al., 2001].

The major strengths of this study are the size of the cohort (n = 67,976 women), the length of follow-up (from 1943 through 1994), and the availability of specific IR exposure levels for over 15% of the cohort. Identification of 91 cases of death from dementia during the follow-up period provided a unique opportunity to evaluate possible associations between occupational exposure to low doses of radiation and the development of dementia. Cases and controls were selected from the same cohort and shared many characteristics.

A major limitation of this investigation is the small number of exposed cases. Quantified radiation exposure data were available for only 14 of 91 cases of death from dementia. Of these 14, only 4 had maximum annual radiation doses ≥5 mSv, while 6 had total lifetime exposures ≥10 mSv. Given the small numbers available for analysis, logistic regression models were limited to main effects. Also, the findings here are limited by reliance on a death certificate diagnosis of dementia. From an occupational health perspective, the main concern is the risk of becoming demented, whether or not the dementia leads to death. An additional limitation is that quantified measures of radiation exposure (i.e., film badge or TLD readings) were available for only one-eighth of this cohort. It is possible that some unmonitored workers received non-trivial exposures to IR. Also, while some workers were monitored for internal radiation exposures, these data were not available for this study.

If the observed association between death from dementia and occupational exposure to IR is replicated, further research will be needed to elucidate the biological mechanism for this effect. Dementia following heavy doses of cranial irradiation has been shown to involve leukoencephalopathy [Filley, 1999] but chronic exposure to low doses in an occupational setting may well have a different physiologic impact. A possible bridge to the known carcinogenic effects of IR is recent research suggesting that AD may be a form of cancer [Habeck, 2001]. A recent review of studies on male nuclear workers [Alexander and DiMarco, 2001] substantiates earlier findings of increased risk for brain tumors in this population. There is also evidence from the radiotherapy literature of hypersensitivity of some tissues to low doses of radiation [Joiner et al., 2001].

The present study provides evidence of an association, in female nuclear workers, between relatively low occupational exposures to external IR and the likelihood of dying demented. These results must be interpreted cautiously, given

[6] Details of this analysis are presented in the Appendix.

TABLE VI. Crude and Adjusted ORs, 95% CIs, and Tests for Trend for Death From Dementia and Exposure to External Radiation in a Pooled Cohort of Female Nuclear Weapons Workers (n = 168)

Exposure	Cases	Controls	Crude OR	95% CI	*P* for trend*	Adjusted OR[a]	95% CI	*P* for trend*
Maximum annual dose (mSv)								
Baseline								
0.0–4.9 (0)	10	140	1.00			1.00		
Stratified								
5.0–9.9 (1)	1	7	2.00	0.22, 18.07		2.44	0.27, 21.80	
10.0–24.9 (2)	2	6	4.67	0.81, 26.85		3.44	0.62, 19.00	
25.0–49.9 (3)	1	1	14.00	0.76, 256.43	0.006	7.60	0.25, 228.91	0.022
Overall								
(0 vs. 1–3)			2.23	1.06, 4.45		2.11	0.98, 4.40	
Total lifetime dose (mSv)								
Baseline								
0.0–9.9 (0)	8	132	1.00			1.00		
Stratified								
10.0–24.9 (1)	3	14	3.54	0.82, 15.18		3.41	0.63, 18.45	
25.0–49.9 (2)	1	3	5.50	0.50, 60.75		—[b]	—[b]	
≥50.0 (3)	2	5	6.60	1.06, 41.10	0.005	8.29	0.38, 178.74	0.003
Overall								
(0 vs. 1–3)			1.99	1.10, 3.46		2.09	1.02, 4.29	

*Score χ^2 test for trend of odds.
[a]Maximum annual dose adjusted for age at risk, years of follow-up, and age first monitored. Total lifetime dose adjusted for age at risk, years of follow-up, age first monitored, and years monitored.
[b]No OR is available for this exposure level due to inadequate data.

the small number of cases and the low doses that were observed. However, it seems advisable for investigators to include cognitive measures in future studies of occupational exposure to IR.

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APPENDIX

Toxic Chemical Exposure

There was potential for exposure to various known neurotoxic chemicals at all study facilities. These included acetone, carbon disulfide, carbon tetrachloride, lithium, mercury, cadmium, lead, nitrogen oxides, sulfur oxides, RDX (1,3,5-triazine), TCE, PCE, benzene, and ethyl ether. Ratings of probable exposure to toxic chemicals were based on the job exposure matrix developed by Wilkinson et al. [2000], with slight modifications, as follows: Minimal likelihood of exposure (code = 0), including only clerical workers; ''low'' likelihood of exposure (code = 1), including kitchen workers, medical workers, sanitation workers, security workers, trainees, and the ''unknown'' category; and ''high'' likelihood of exposure (code = 2), including artists, chemists, construction workers, electricians, machinists, nuclear workers, technical workers, and transportation workers.

A total toxic chemical exposure score was calculated for each worker by multiplying the exposure code for each job held by the number of years spent in that job. For women holding jobs with different exposure levels, separate scores were calculated for each job and then summed.[7] Total scores ranged from 0 to 100. For purposes of analysis, these scores were collapsed to two categories: 0–1 and $\geq$2. A score of 0–1 represents no more than 1 year in a job with ''low'' likelihood of exposure to toxic chemicals, while a score $\geq$2 indicates at least 1 year in a job with a ''high'' likelihood of toxic chemical exposure or at least 2 years in a ''low'' exposure job. Sixty-two percent of the workers studied fell in the 0–1 category.

If exposure is defined as a total score $\geq$2, there is a slightly higher proportion of ''exposed'' cases (41.5%) than of ''exposed'' controls (36.9%). The crude odds ratio (OR) comparing ''exposed'' with ''unexposed'' workers based on these data is 1.21 (95% CI = 0.74, 1.97). When the potential association of toxic chemical exposure with death from dementia is evaluated in a comprehensive logistic regression model, controlling for age at hire, years worked, age at censoring, and years of follow-up, OR = 1.42 (95% CI = 0.84, 2.40).

[7] This methodology was reviewed and approved by Dr. Norman Trieff, the industrial hygienist who developed the Wilkinson et al. [2000] job exposure matrix.