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Brain tumors and occupational risk factors - a review

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separation of a uranium isotope through an electromagnetic process and other engineering and manufacturing processes in the fabrication of nuclear weapons.

Workers employed in the manufacture, chemical separation, and purification of plutonium at the Hanford plant in Washington state did not have an elevated brain cancer risk (22) overall (table 7) or in any cumulative radiation dose category. Data for men in metalworking and machining occupations were not shown separately.

None of the studies at nuclear weapons fabrication facilities showed an association of elevated brain cancer risk in relation to any particular radiation level. One factor common to all of the facilities was the presence of machining operations in which there was an opportunity for exposure to metal dusts and fumes and lubricating oil mists. Beryllium was machined at one of the facilities (102).

Other industrial workers

Numerous chemicals, some of which contain formaldehyde, are used in photographic processing operations, and high levels of formaldehyde have been measured in print laboratories (21). After preliminary studies indicated a possible brain cancer excess among employees of an Eastman Kodak plant, a nested case-referent study of brain cancer by exposure category indicated an elevated risk among photographic processing workers exposed to color developers (24). Risks were slightly elevated among workers exposed to solvents, animal tissue, and film developers (table 8). None of the results were statistically significant. No deaths from brain cancer were observed among 208 deceased white male press photographers who often developed their own film (49).

A study of 47 glioma cases diagnosed in 1979 and 1980 in Milan, Italy, indicated a twofold excess risk of glioma among textile workers (55). The odds ratio of 2.1 was not statistically significant (table 8). About 20 % of the cases had worked in the textile industry, where formaldehyde and other chemicals were used in processing fabrics. In a 1950 survey, US men employed in yarn, thread, and fabric mills had an elevated standardized mortality ratio for brain cancer (26).

White male members of the Pattern Makers League of North America who died between 1972 and 1978 had an increased relative frequency of brain tumor deaths (68). The proportionate mortality ratios were elevated among pattern makers who worked predominantly with wood and among those who worked predominantly with metal (table 8). A cohort analysis of cancer morbidity among automobile pattern makers who worked with wood found no significant excess of brain cancer (79).

Machinists employed at an automobile manufacturing plant for five years or more in jobs with exposure to cutting oil mists did not have a significantly elevated risk of death due to brain cancer (O:E = 5:3.3) (13). Among men who entered the study group after 1948,

Table 8. Brain tumors among other industrial workers.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Kodak workers (age 55—59 years), NY	1964—1975	SIR	14	2.81*	Greenwald et al (24)
Kodak workers — solvents	1956—1975	OR	32	1.40	Greenwald et al (24)
Kodak workers — color developers	1956—1975	OR	6	2.16	Greenwald et al (24)
Kodak workers — animal tissue	1956—1975	OR	13	1.32	Greenwald et al (24)
Kodak workers — black & white developers	1956—1975	OR	7	1.31	Greenwald et al (24)
Textile workers, Italy	1979—1980	OR	10	2.1	Musicco et al (55)
Yarn, thread, fabric mills, US	1950	SMR	32	1.45	Guralnick et al (26)
Pattern makers — wood, US	1972—1978	PMR	7[d]	1.75	Robinson et al (68)
Pattern makers — metal, US	1972—1978	PMR	5[d]	2.94	Robinson et al (68)
Automobile wood pattern makers, MI	1970—1978	SIR	1	1.63	Swanson & Belle (79)
Automobile machinists (1948+), US	1937—1967	SMR	3	3.75	Decoufle (13)
Aviation electronics workers, US	1950—1980	PMR	9	3.01*	Sweeney & Ahrenholz (80)
Aluminum reduction workers, US	1946—1976	SMR	8[d]	2.25	Milham (47)
Bus mechanics, UK	1967—1975	SMR	4	3.20	Rushton et al (72)
Railroad carmen, Canada	1965—1977	SMR	7	2.78*	Howe et al (32)
Railroad — welding fumes, Canada	1965—1977	SMR	10	3.18*	Howe et al (32)
Railroad workers, US	1967—1979	SMR	5	1.32	Schenker et al (73)
Asbestos insulation workers, US	1967—1976	SMR	21[d]	1.59	Seidman et al (76)
Electricians, linemen, servicemen, engineers, MD					
Glial tumors	1969—1982	OR	27	2.15*	Lin et al (38)
Unspecified brain	1969—1982	OR	15[d]	1.54	Lin et al (38)

[a] NY = New York, US = United States, MI = Michigan, UK = United Kingdom, MD = Maryland.
[b] See table 1 (footnote b) for a definition of the abbreviations.
[c] Ratio = observed:expected ratio or odds ratio.
[d] Observed includes benign and unspecified brain tumors.
* Statistically significant (Poisson) at the 0.05 level.

however, there was a notable excess of brain cancer deaths (table 8).

A proportionate mortality ratio analysis indicated that white male hourly and salaried employees of an aviation electronics plant had an elevated frequency of deaths from brain cancer (table 8) (80). Six of the nine brain cancers were glioblastoma multiforme, one was neurilemmoma, and two were unspecified. Potential workplace exposures included trichlorethylene, beryllium, and a halogenated aromatic hydrocarbon balancing fluid. All five hourly employees with brain cancer had worked as machinists.

A mortality study of aluminum reduction plant workers (table 8) indicated an elevated risk of benign brain tumors (observed 5, SMR 9.09) but not malignant tumors (observed 3, SMR 0.99) (47). All five persons with benign brain tumors had worked in "exposed" jobs in the carbon plant, rodding, potlining, potrooms, or quality control. Exposures included fluorides, particulate alumina, polycyclic aromatic hydrocarbons, and sulfur dioxide. An excess of benign neoplasms was found in another study of workers employed in 14 aluminum reduction plants (69); however no details were given regarding the primary site of these tumors.

Maintenance workers exposed to hydrocarbons in the form of diesel exhaust in London bus garages had a slightly elevated standardized mortality ratio for brain cancer (SMR 1.21) (72). This excess was primarily due to the elevated standardized mortality ratio for brain cancer among bus mechanics, who were also exposed to oils, greases, and solvents (table 8).

A study of Canadian railroad workers exposed to diesel fumes and coal dust showed an elevated brain cancer risk among carmen (table 8) (32). Railroad workers exposed to welding fumes had a threefold excess of brain cancer mortality. A survey of mortality by occupation in Sweden also showed excess brain cancer among welders (table 2) (18). US railroad workers had a slightly elevated standardized mortality ratio for brain cancer (table 8), but no data were shown for those with high levels of exposure to diesel or welding fumes (73).

A slightly elevated brain tumor risk was reported in a cohort study of asbestos insulation workers (table 8) (76). These workers were employed primarily in the building construction trades, but they also could have worked in shipyards, chemical plants, and oil refineries, where there are exposures to numerous substances.

A case-referent study using the occupation listed on death certificates suggested an elevated risk of glioma and unspecified brain tumors among a category of workers which included electric and telephone company servicemen, linemen, foremen, and engineers; railroad and telecommunication engineers; electricians; and electric and electronic engineers (table 8) (38). These findings are consistent with those seen in four surveys of mortality by occupation (table 2) that found elevated brain cancer mortality among electricians and power servicemen. Electrical engineers (table 1) also had elevated brain cancer mortality. These occupations have potential exposure to electromagnetic fields, polychlorinated biphenyls, solder fluxes, and solvents.

Professional and other nonindustrial groups

The National Institute for Occupational Safety and Health (NIOSH) evaluated the mortality experience of white men employed as motor vehicle examiners in New Jersey for at least six months between 1944 and 1973 (77). The examiners were exposed daily to motor vehicle exhaust consisting of aldehydes, carbon dioxide, carbon monoxide, hydrocarbons, lead compounds, nitrogen, oxides of nitrogen, oxygen, and sulfur dioxide. Four deaths from brain cancer were observed, and only 1.7 were expected (table 9). All four brain cancers were malignant gliomas.

A proportionate mortality ratio study of professional artists indicated a significant threefold excess frequency of brain cancer deaths among white male artists (table 9) (50). The excess deaths were not linked to any particular art specialty. Artists may be exposed to numerous potentially carcinogenic substances including components of pigments, dyes, solvents, metal fumes, and dust.

Professional chemists are exposed to numerous chemical agents in the laboratory setting. An elevated standardized mortality ratio for brain cancer was seen among 526 chemists who had been educated at one school in Sweden (58) between 1930 and 1949. No brain cancer deaths occurred among 331 men educated at a second Swedish school (58). Further follow-up of the first cohort indicated a significantly elevated mortality from brain cancer (table 9) (59). Other studies of chemists have not reported elevated brain cancer mortality (31, 37).

Members of the Royal College of Pathologists in 1973 were followed for vital status in 1981 (30). Among 2 300 men, six deaths from brain cancer occurred and less than two were expected (table 9). Hematology was a common subspecialty among the decedents with brain cancer. Pathologists are exposed to formaldehyde and other laboratory chemicals. Anatomists, who are exposed to similar chemicals, had a significantly elevated brain cancer risk (78) compared with the US general population (table 9). When another professional group was used for a comparison, the standardized mortality ratio was 6.00. Risk appeared to increase by duration of employment, but was also elevated among those employed less than 20 years. Risk was elevated regardless of presumed level of exposure to formaldehyde. Four of the 10 brain cancers were listed as "astrocytoma" on the death certificate, while the remaining six were listed as "glioblastoma."

Proportionate mortality ratio analyses of deaths among embalmers and funeral directors in New York

Table 9. Brain tumors among professional and other nonindustrial workers.

Occupation or type of work[a]	Study period	Measure of association[b]	Observed brain tumor events	Ratio[c]	Reference
Moto vehicle examiners, NJ	1944—1973	SMR	4	2.35	Stern et al (77)
Professional artists, US	1940—1969	PMR	8	2.90*	Miller et al (50)
Chemists — one school, Sweden	1930—1977	SMR	5	4.17*	Olin & Ahlbom (59)
DuPont chemists, US	1964—1977	SIR	2	0.67	Hoar & Pell (31)
Pathologists, UK	1974—1981	SMR	6	> 3.00*	Harrington & Oakes (30)
Anatomists, US	1924—1979	SMR	10	2.71*	Stroup et al (78)
Embalmers, NY	1925—1980	PMR	6	2.34	Walrath & Fraumeni (93)
Embalmers, CA	1925—1980	PMR	9	1.94	Walrath & Fraumeni (94)
Embalmers, Ontario	1950—1977	SMR	3	1.15	Levine et al (36)
Female cosmetologists, CT	1935—1978	SIR	16	1.68	Teta et al (86)
Registered female nurses, WI	1963—1977	PMR	21	1.61	Katz (34)
Veterinarians, US	1947—1977	PMR	28	1.63*	Blair & Hayes (7)
Farmers after 1960, Italy	1979—1980	OR	13	3.6*	Musicco et al (55)
Agricultural industry, Canada	1965—1973	SMR	4	2.68	Howe & Lindsay (33)
Agricultural workers, Sweden	1961—1973	SMR	744	1.08*	Wiklund (101)

[a] NJ = New Jersey, US = United States, UK = United Kingdom, NY = New York, CA = California, CT = Connecticut, WI = Wisconsin.
[b] See table 1 (footnote b) for a definition of the abbreviations.
[c] Ratio = observed:expected ratio or odds ratio.
* Statistically significant (Poisson) at the 0.05 level.

(93) and California (94) indicated elevated frequencies of brain cancer deaths (table 9). Among white men in New York licensed only as embalmers, there was a 2.5-fold excess (93). A cohort mortality study of Ontario embalmers did not show an excess brain cancer risk, but the study group was small, and no data were shown by latency or duration of exposure (36). Embalming fluids consist primarily of formaldehyde, but also contain phenol and methanol.

Professional cosmetologists are occupationally exposed to numerous chemical substances, including formaldehyde solutions, hair dyes, permanent wave solutions, and other cosmetic preparations. Female cosmetologists in Connecticut had an elevated incidence of brain cancer (table 9) (86). This excess was more prominent among those who began hairdressing school between 1925 and 1934 (observed 6, SIR 2.02). Ten of the 16 cases observed were histologically confirmed glioblastoma multiforme.

A significantly elevated frequency of nervous system cancers was seen among registered nurses in Wisconsin in a comparison with other gainfully employed women (table 9) (34). The observed number of deaths was also greater than the number expected on the basis of mortality among other female professional workers (PMR 1.47).

An analysis of mortality among veterinarians indicated an excess frequency of deaths from brain cancer (table 9) (7). The increased relative frequency was not confined to any particular veterinary specialty group.

Four studies have shown an elevated brain cancer risk among farmers (table 9). Odds ratios for gliomas were statistically significant among Italian farmers who had been farming for more than 10 years and among those who had been engaged in farming since 1960, when the use of phosphoric acid and organochlorine compounds became very common as pesticides in Italy (55). A study of primary CNS neoplasms in Minnesota indicated a slightly higher than expected proportion of farm residents among the brain tumor cases (10). The authors speculated that there may be an association with toxoplasmosis gondii infection. Elevated brain cancer risk was also found in a study of Swedish agricultural workers (101) and among agricultural workers in Canada (33).

Discussion

There were several limitations in the presented epidemiologic studies. First, there is a paucity of case-referent studies of brain tumors; thus most of the information was obtained from mortality studies that lacked sufficient statistical power to evaluate specific occupational risk factors adequately for brain tumors. The observed and expected numbers of brain tumor cases in most of the studies were very small. Exposure information was ascertained from work histories in some of the studies and from interview data in some, but, in others, no specific information on workplace exposures was available. In the nested case-referent studies the numbers were very small, and there were difficulties in relating exposures to specific jobs. In most instances workers had multiple exposures, and risks due to any single exposure could not be adequately evaluated.

Brain tumor diagnosis was ascertained from death certificates in most of the studies; therefore the accuracy of the diagnoses may be questionable. The diagnosis "brain tumor" listed on a death certificate would be nosologically coded as a primary tumor of the brain, unspecified as to whether malignant or benign. Many of these tumors may actually have been primary malignancies of the brain. Alternatively, since the brain is a common site for metastases of other primary cancers, some death certificate diagnoses may not reflect the actual primary site. A study of deceased persons in the Third National Cancer Survey areas indicated that about 97 % of deaths from malignant brain tumors would be ascertained from death certificates (62), whereas only 89 % of all primary brain cancer diagnoses on death certificates were confirmed by hospital records. This finding indicates that about 10 % of the brain cancer cases ascertained from death certificates may be misdiagnosed. The issue of misdiagnosis is not considered a major problem, particularly if the general population is used to calculate expected numbers of death in studies that ascertain cause of death from death certificates.

In 1981 Greenwald et al (24) concluded that an excess of brain tumors noted among Kodak employees may have resulted from a "diagnostic sensitivity bias." This conclusion was drawn because none of the results of the nested case-referent study were statistically significant and because Kodak employees had brain tumor diagnoses that were histologically confirmed more often than did other brain tumor patients in New York. This explanation might appear plausible in light of the excess risk noted in several professional and white-collar groups; however, all of the workers reported to have elevated brain tumor risk in this review were probably not enrolled in comprehensive medical surveillance programs. Furthermore excess brain tumors were seen only among certain subgroups of some plant populations (eg, workers in the tire building sector of rubber production, refinery workers in lubricating oil manufacture). In addition other groups with medical surveillance programs, for example, Du Pont employees, do not show an elevated brain tumor risk (61).

Despite limitations in study methodology, some similarities are seen between the findings of these studies with respect to age and cell type diagnoses. Ages at death for most of the brain tumor cases ranged between 40 and 65 years. It is not clear whether this pattern reflects the age distribution of the populations studied or a biological phenomenon related to the origin of brain tumors. Age-specific mortality rates for US white males indicate a peak between the ages of 45 and 65 years (45).

Very few studies included diagnostic information from sources other than death certificates. Since death certificates do not often indicate the cell type of these tumors, most studies grouped all brain tumors without distinction by cell type. It is possible that risk factors vary by cell type. In the studies that had diagnostic information from medical records, a high percentage of the diagnoses were gliomas, particularly glioblastoma multiforme; however, no expected numbers could be calculated for this type.

Table 10 shows selected categories of exposures common to the work environments of the occupational groups that appear to have an elevated brain tumor risk. This list is by no means all-inclusive, and one must keep in mind that most of the occupational groups listed are exposed to multiple agents. Numerous groups with elevated brain tumor risk are likely to be exposed

Table 10. Common ocupational exposures among groups with elevated brain tumor risk.

Occupational group potentially exposed	Exposure					
	Organic solvents	Lubricating oils	Acrylonitrile or vinyl chloride	Formaldehyde	Polycyclic aromatic hydrocarbons	Phenols and phenolic compounds
Acrylonitrile polymerization workers	×	.	×	.	.	.
Airplane mechanics and repairmen	×	×	.	.	×	.
Aluminum reduction plant workers	×	.	.	.	×	.
Anatomists	.	.	.	×	.	×
Artists	×	.	.	.	.	.
Bus mechanics	×	×	.	.	×	.
Chemists	×	.	.	.	.	×
Cosmetologists	.	.	.	×	.	×
Electricians	×	.	.	.	.	.
Embalmers	.	.	.	×	.	×
Farmers and agricultural workers	×	×	.	.	.	×
Formaldehyde production workers	.	.	.	×	.	.
Machinists	×	×	.	.	×	.
Motor vehicle examiners	.	.	.	.	×	.
Nuclear fuels & weapons fabrication	×	×	.	.	×	.
Nurses	.	.	.	.	.	×
Oil refinery workers	×	×	.	.	×	×
Pathologists	.	.	.	×	.	×
Pattern makers — metal	×	×	.	.	.	.
Petrochemical plant workers	×	.	.	.	.	×
Pharmaceutical workers	×	.	.	×	.	×
Photographic process workers	×	.	.	×	.	×
Polyvinyl chloride production workers	×	.	×	.	.	.
Rubber workers	×	.	×	.	×	×
Textile workers	×	.	.	×	.	×
Veterinarians	.	.	.	×	.	×

to organic solvents. This broad category of compounds includes aliphatic hydrocarbons and aliphatic halognated hydrocarbons like methylene chloride, carbon tetrachloride, tetrachloroethylene, and others. It also includes aromatic hydrocarbon solvents like benzene and toluene. One of the common acute effects of exposure to many of these compounds is CNS depression (16); however solvents are not known to cause brain tumors experimentally. Oil refinery workers, chemical plant workers, rubber workers, and many other occupational groups are exposed to organic solvents.

Exposure to polycyclic aromatic hydrocarbons occurs in the rubber manufacturing, petroleum refining, and aluminum reduction industries. Motor vehicle examiners and bus mechanics may also be exposed to these hydrocarbons in motor vehicle exhaust. Certain polycyclic aromatic hydrocarbons have induced brain tumors in animals by direct implantation and transplacentally, but not by inhalation exposure (81).

Lubricating oils produced by oil refineries are used for maintaining mechanical equipment and machines and for lubricating cutting edges. Thus several of the groups with elevated brain cancer mortality are exposed to various types of lubricating oils.

Gliomas have been experimentally induced in animals by inhalation exposure to acrylonitrile and vinyl chloride (40, 41). These compounds are similar in chemical structure and are found in plastics departments in the rubber industry, in polyvinyl chloride production, and in acrylonitrile polymerization.

Formaldehyde has recently been shown to induce nasal cancer in rats (82), a finding implying that it may also be carcinogenic in humans. Several of the groups with elevated mortality from brain cancer were occupationally exposed to formaldehyde. These groups include blue-collar workers involved in formaldehyde production, photographic processing and textile production, professionals who use formaldehyde in the laboratory setting, and embalmers.

Phenols and phenolic compounds are used widely in manufacturing industries, and many of the compounds have commercial uses. These include phenol, chlorophenols, cresol, resorcinol, hydroquinone, and quinone. Phenolic compounds are used in the production of explosives, fertilizers, textiles, paints and paint removers, rubber, wood preservatives, synthetic resins, pharmaceuticals, photographic chemicals, rubber, and organic chemicals. Commercial uses include fungicides and herbicides, disinfectants, laboratory reagants, and photographic processing (60). Acute intoxication of these compounds causes severe CNS effects, including tremors, convulsions, vertigo, and mental disturbances. None of these compounds have induced brain tumors experimentally; however some phenols are known to be tumor promoters and cocarcinogens in certain tissues (16).

Of the broad categories of aforementioned substances, only a few have been shown to cause brain tumors in laboratory animals. These include certain polycyclic aromatic hydrocarbons, vinyl chloride, and acrylonitrile. However, several of the substances, specifically, formaldehyde, certain solvents, and some phenolic compounds, are known to cause neurotoxic effects after acute high-level exposure. Thus, the brain is obviously a target organ for the toxic effects of these materials.

Clearly, further epidemiologic studies are necessary to evaluate the relationship between brain tumors and occupational exposures. These studies should include large numbers of cases and diagnostic confirmations so that data may be analyzed by cell type. Sufficient care should be used in selecting referents so that the diagnostic sensitivity problem, if it exists, is minimized. Finally, and most importantly, an attempt should be made to develop detailed occupational exposure indices.

NOTE: Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the United States Department of Health and Human Services.

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