Occupational Cancer of the Nervous System

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The occurrence of nervous systems cancers has increased markedly over the past 40 years, particularly brain tumors among white males over the age of 55, which has raised the possibility of occupational contributions to etiology. In fact, there has accumulated enough evidence to suggest that a link may exist between the incidence of brain tumors and certain occupations and chemical exposures. The first inkling of this came from animal studies in the early 1940s that demonstrated the induction of brain tumors in rats by direct intracranial implantation of known carcinogens. Subsequent studies in rats demonstrated that gliomas could be induced by inhalation or ingestion of acrylonitrile, whereas neuroblastomas developed with vinyl chloride inhalation. These and similar compounds have been used extensively in the plastics and rubber industries. Later epidemiologic studies, particularly in rubber workers, suggested that humans with certain industrial exposures may indeed be at increased risk for developing brain tumors. These investigations prompted research in other industries and there are now studies raising concern of a potential excess risk for brain tumors in a number of work-related environments including rubber manufacturing, polyvinyl chloride production, oil refining and petrochemical production, and nuclear fuels and weapons fabrication. Unfortunately, in many cases the evidence is conflicting and inconclusive, and further study is necessary, but epidemiologic analysis has been complicated by lack of complete exposure data, prolonged latency periods, and difficulty in obtaining and accounting for different histologic cell types.[1,2]

RUBBER MANUFACTURING

Mancuso's studies on synthetic rubber workers arose following his observation that the 1947 death certificates among white males between the ages of 25 and 64 in Summit County, Ohio (the location of most of the U.S. tire manufacturing at the time) revealed an excess proportional mortality for brain cancer.[3] Mancuso went on to determine that men employed in tire assembly and tire curing had a particularly elevated risk for developing brain/CNS malignancies, although a lower than expected risk existed for the entire plant populations.[3] Although potentially toxic chemicals including coal tar, carbon disulfide, benzene, and other solvents had been used in the tire manufacturing process, none of these compounds could be directly linked to CNS carcinogenesis. Nevertheless, subsequent studies by Monson et al. supported Mancuso's original observations.[4,5]

However, later investigations, including a large cooperative study that used a cohort of active and retired male workers between 1963 and 1973 from 48 different plants, failed to support the earlier findings.[6] Other cohort studies after 1964 were also unrevealing.[7,8] It has been argued that the earlier studies were representative of exposures initially found in the rubber tire manufacturing process that have since been removed.

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POLYVINYL CHLORIDE PRODUCTION

When it was first reported that workers exposed to high levels of vinyl chloride were at increased risk for developing angiosarcoma of the liver, an otherwise rare tumor, NIOSH and other study groups intensified their investigations in order to identify other possible hazards from exposure. Waxweiler et al. reported that among a cohort of workers exposed to vinyl chloride for greater than 15 years, a significant risk for the development of brain cancer existed with three observed and 0.6 expected.[9] Overall, a total of ten brain cancers were identified among vinyl chloride workers on the basis of death certificates, pathology reports, and/or tissue evaluation, and nine of the ten brain tumors were histologically identified as glioblastoma multiforme; no histologic diagnosis was available on the tenth.[9] Although glioblastoma multiforme is a brain tumor that occurs in a relatively high proportion of adult cases, this percentage is considerably higher than would be expected. Furthermore, a proportional mortality ratio of 4.2 was calculated from a study by Monson on deceased workers from two plants with vinyl chloride monomer exposure.[10] At about the same time, Maltoni et al. were able to show that brain tumors could be induced in rats when exposed to vinyl chloride by inhalation at levels resembling the human exposure data.[11,12]

In Britain, Fox and Collier observed two brain cancer deaths as compared to 3.7 expected for a cohort of vinyl chloride exposed workers.[13] However, of the cohort members that were considered to have a high exposure, one brain cancer death was observed versus 0.4 expected. Although the number of brain tumor cases in all these studies is relatively small, the results are generally regarded to be indicative of an association between vinyl chloride exposure and the development of brain malignancy, in particular glioblastoma multiforme.

OIL REFINING AND PETROCHEMICAL PRODUCTION

There has been considerable effort by numerous study groups to determine if oil refining and petrochemical production could be linked to brain cancer. Although the potential carcinogenicity of certain petroleum products is well established, the cancer risk among refinery workers is less clear-cut. In the United States, the focus came about when representatives of Union Carbide and the Oil, Chemical and Atomic Workers Union together identified 18 cases of brain cancer among deceased and living former employees of the Union Carbide plant in Texas City, Texas.[14] Epidemiologists from OSHA/NIOSH joined the effort with a cohort mortality study on workers employed at Union Carbide and consequently found a significantly increased SMR of 2.06 for white male hourly workers at the same Union Carbide plant.[15] In addition, Reeve et al. from NIOSH found that residents of Brazoria County, the site of Dow Chemical, had a twofold risk of dying from a brain tumor if, at any time, they had worked at the Dow petrochemical plant.[16] However, Ralph Cook, the director of epidemiology at Dow, and his group failed to find an association between a specific job category or exposure with an elevated risk for developing brain tumors among employees at Dow.[17]

Subsequently, Thomas et al. from the National Cancer Institute calculated a proportional mortality ratio for brain tumors of 2.28 in deceased active and retired members of the Oil, Chemical and Atomic Workers Union among hourly workers employed at Mobil, Gulf, and Texaco petroleum plants in the Beaumont-Port Arthur area of Texas.[18] However, a series of industry-based studies of the same three refineries found no increased risk.[19–21] No association between brain tumors and specific work categories was demonstrated in a follow-up case-control study by Thomas et al.[22]

In 1980, J. William Lloyd of OSHA and Irving Selikoff of the Mount Sinai School of Medicine organized a conference through the offices of the New York Academy of Sciences in order to evaluate the rapidly growing but conflicting evidence on brain tumors and exposure to petrochemical production. Several studies were presented including four by epidemiologists from OSHA, NIOSH, and NCI and four by investigators with industry-backed support (Dow Chemical, Gulf Oil, DuPont, and a group representing some of the United Kingdom oil refineries). The disparities were marked with the government studies invariably indicating a twofold increased risk and the industrially supported studies showing no elevation of risk. The industry-backed studies were criticized for including all employees such as office workers who were most likely not significantly exposed. By diluting the study population, certain subgroups who actually had significant exposures and potential risks may not have been identified. On the other hand, some of the criticisms pertaining to the government studies that were brought out included the use of PMR methodology which can inflate the calculated risk for cancer. Some of the problems faced by all the investigators included the relatively low number of identified cases, the varied degree of exposures among employees, and the retrospective analysis that involved tracing employee records back through 40 or more years.[23]

Most recently, a five-year follow-up of a previous mortality study on 1,207 men employed in a Canadian oil refinery again revealed an excess risk of brain malignancies (SMR = 519) among men who died within 20 years of first exposure.[24] The study, however, failed to identify any hazardous exposures in the workplace

Although conflicting results exist concerning the increased risks for brain malignancies in the oil refining and petrochemical production process, there is enough

evidence to suggest such a risk. The extremely large size of the work force together with the controversial study results place a great demand on investigators to proceed with further research.

OTHER INDUSTRIAL AND NONINDUSTRIAL STUDIES

The results of some of the above studies have prompted investigations in other industries including the nuclear fuels and weapons fabrication industry. In one study, the mortality risk was found to be elevated (SMR = 2.40) and the incidence rate was found to be significantly elevated (SIR = 2.67) for brain tumors among male employees at a nuclear fuel fabrication plant. However, radiation, industrial, or previous employment exposures could not be correlated.[25] Uranium fuel is contained in a controlled area and the radiation levels are assumed to be low; however, the exposures to metal dust, fumes, and oil mists are not unlike a metal fabrication plant and have to be considered as well as possible sources of carcinogen exposure in nuclear fuel fabrication. At the Rocky Flats Nuclear Plant, Wilkenson et al. noted an increased risk for brain tumors, however, when tumors of benign and unspecified classifications were excluded, the increased risk was no longer statistically significant.[26] Other studies of plutonium processing workers failed to demonstrate an excess brain cancer risk among employees.[27] However, because the nuclear industry is still relatively new, the latency period may be insufficient to accurately examine the risks in these cohorts. Follow-up investigations on already studied cohorts would certainly be worthwhile, particularly because studies of other groups nonoccupationally exposed to radiation for medical-diagnostic and therapeutic purposes support the concept of radiation-induced nervous system tumors.[2]

Several other occupationally or environmentally exposed groups have been targeted as potential risks for brain malignancies. Professional artists, pathologists, embalmers, and farmers are examples of the nonindustrially exposed groups with suspected brain tumor risks.[28] Chemicals common to these groups include formaldehyde and organic solvents although definitive correlations with exposure have not been established. In addition, farmers are exposed to pesticides, and Italian studies have suggested that this may be contributory to the increasing incidence of gliomas in this occupational group.[29] Other potential associations that have been noted include: trauma and the development of brain tumors, particularly meningiomas; lead exposure and the development of astrocytic gliomas in children and animals; dietary consumption of nitrites and meningiomas in women; exposure to farm animals and the development of childhood brain tumors (suggesting a possible role of animal viruses)[2]; and occupational or environmental exposure to power frequency magnetic fields and brain tumors.[30,31]

One of the most serious problems with occupational studies of nervous system tumors in the past has been the failure to segregate out the various and diverse histologic types owing to lack of adequate pathologic evidence and the small numbers involved. However, it is probably erroneous to consider all primary nervous system tumors as a single disease in terms of susceptibility to induction by occupational exposures. The most recent studies have attempted to address this issue. For example, a case-control study of 78 astrocytoma patients showed an elevated risk for working at an airfield or living near a petrochemical plant, sewage treatment plant, or paper or saw mill.[32] A study based on the Swedish Cancer-Environment Registry examined 1,092 cases of meningioma and found statistically significant standardized incidence ratios between 4.7 and 6.0 for glass, porcelain or ceramic workers of both sexes, and for male workers in headgear fabrication and book publishing. Significant SIRs between 1.7 and 3.0 were observed for men employed in health care, railroad and trolley construction, sheet and plate metal fabrication, moving equipment operations, and elementary schools.[33] These findings were consistent with previous studies.[28,34–37] In a parallel study of intracranial gliomas, a significant twofold excess risk was also found for glass, porcelain, and ceramic workers.[38] This group is of interest because of potential exposure to arsenic, chromium, and lead, and hat makers are of interest because of potential exposure to mercury, a well-known neurotoxin.

Finally, note should be made of the concern for the potential development of childhood brain tumors due to parental occupational exposures.[39] It has been clearly demonstrated in animal models that carcinogen exposure in the mothers can cause brain tumors in the offspring. For example, the offspring of pregnant rats injected intravenously with ethyl nitrosourea during the latter half of pregnancy have an increased incidence of gliomas and neuromas; in fact, the nervous systems of fetal rats have a 50-times-greater sensitivity to the carcinogenic effects of ethyl nitrosourea compared to adults.[40] The first indication of a possible effect in humans was provided by the study of Fabia and Thuy which raised the possibility that children of fathers in hydrocarbon-related occupations were at elevated risk for childhood cancer, a large fraction of which occur in the nervous system.[41] Hemminki et al. found an association between brain cancer in children under 15 years old and specific jobs held by the father, including machine repairmen (relative risk = 4.4) and painters (relative risk = 2.6), once again raising the possibility of a link to hydrocarbon and other chemical exposures.[42] Other studies have supported an association with parental chemical exposure or work in particular industries

(metal and construction work) with the development of childhood tumors.[43–45] Design problems common to these studies have included confounders, histologic diagnosis and the vagueness of job category. The independent risk factors not addressed have included pre- or postnatal radiation exposure, cancer in siblings, viral diseases, and congenital defects. Although none of the findings warrant a firm conclusion, clearly, as is true with occupational associations for nervous system cancers in general, further investigation is warranted

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