Brain Cancer: Peer-Reviewed Analysis

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Brain and Central Nervous System Tumors

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Brain tumors may involve either the spinal cord or brain, and include a variety of cell types that have different patterns of occurrence, different outcomes, and may have different causes. The most common types of brain tumors are gliomas, arising from structural, non-neural cells in the brain, and accounting for about 60% of primary malignant brain tumors overall. These cancers are frequently highly invasive. Meningiomas, arising from the covering around the brain or spinal cord, account for about 20% of brain cancers and are generally more benign. Specific types of tumors can also arise in the pituitary gland, the pineal gland, or the vestibular nerve.

Brain tumors are the second most common form of cancer in children, and are the leading cause of cancer death in children under age 20, now surpassing acute lymphoblastic leukemia (ALL) (American Cancer Society 2000). Boys are more likely to develop central nervous system tumors than girls (Gurney et al. 1999). Brain cancers are increasing in children. From 1973 to 1994, the number of reported brain tumors in children under 15 increased 1.8% per year (Smith et al. 1998). In adults, the number of brain tumor cases in the U.S. and Europe has increased by up to 40% over the past 20 years. The rates have increased among people of all ages, but males between the ages of 20 and 40 are the most affected (Lorenzi 2003). Brain cancers are the third leading cause of cancer death in young adults ages 20-39 (Ries et al. 1999).

Many scientists believe that the reported increase in brain tumors is due to improved detection of the disease through use of CT (computerized tomography) and MRI (magnetic resonance imaging) (Smith et al. 1998; Smith et al. 2000). These scientists point particularly to the increases in diagnosed brain tumors in the elderly and contend that in the past these tumors would never have been diagnosed. Other scientists argue that the increase is not likely to be fully explained by improved diagnosis, especially in children, because in young people brain tumors do not go undetected for very long, regardless of the method used (Kaiser 1999). Moreover, the increase appears to have continued for many years (Bleyer 1999). If the increase were due entirely to improved detection, one might expect to see a plateau and then a reduction in new cases once the better detection method is adopted.

Known and Suspected Causes of Brain and Central Nervous System Cancer

Causes of these tumors are largely unknown. Some rare genetic syndromes are associated with a higher risk of childhood brain tumors, as is radiation exposure, but these causes account for only a tiny fraction of the disease (Bunin 2000). Several large studies have reported that gliomas are less likely to occur in people with allergies and in people who have had infections with common viruses such as that which causes chicken pox, implying that immunological factors may be involved (Wrensch et al. 2001). Some evidence suggests that people who have had serious head injuries may be at increased risk of subsequently developing a brain tumor near the site of the original injury (Wrensch et al. 2002).

Ionizing radiation is the only established environmental cause of brain tumors (Preston-Martin 1996). Occupational exposure to radiation has been consistently linked to adult brain tumors (Alexander and DiMarco 2002), and has also been linked to childhood brain tumors in the offspring of people exposed to radiation at work. One study looking at geographic and time-related patterns of brain tumors in children found that rates of the disease significantly decreased in downwind communities when nuclear power plants ceased their operations (Mangano et al. 2002). Other environmental agents that have been suggested as contributing to this type of cancer include pesticides, solvents, electromagnetic fields (including cell phones), and nitrosamines that may be created in the digestion of processed meats such as bacon, ham, and sausages (Preston-Martin et al. 1996).

Because brain tumors are fairly rare, studies looking for environmental causes face serious challenges. If the studies try to focus on specific types of brain tumors, they must include a very large number of people in order to achieve statistically reliable results. If, on the other hand, they lump all types of gliomas, meningiomas, and other brain cancer types together, they may miss important links between specific exposures and specific tumor types, especially since these different types of brain tumors have different occurrence patterns. Assessment of exposures in brain cancer studies is another serious problem. Many studies use occupation to try to predict possible chemical or radiation exposures, but people who work in the same industry do not necessarily share the same exposures, and all workers are exposed to a variety of substances at work and at home. Researchers also do not know for sure how many years it takes a brain cancer to develop. It is difficult to design studies looking at past environmental exposures when the critical time period is not known. Finally, many retrospective epidemiological studies may be weakened by a phenomenon known as recall bias, which can create false associations between exposures and a disease. People who have a serious illness are more likely to make the effort to remember past exposures than are healthy people. So even those studies that do find significant associations between environmental factors and brain tumors must be viewed with some degree of skepticism.

Pesticides

Adult Brain Tumors and Pesticides: Farmers have a higher risk of brain cancer compared to the general population (Blair et al. 1985). A meta-analysis of 33 studies done from 1981-1996 on this topic showed a 30% increased risk of brain cancer among farmers (Khuder et al. 1998). Some researchers have proposed that the increased risk may be related to pesticide exposure (Viel et al. 1998). Farmers, however, are also exposed to factors other than pesticides, such as dusts, animals, animal viruses, and petrochemical products (Bohnen and Kurland 1995). It has been difficult to sort out these different possible factors in the studies that have been done so far. Some studies have attempted to clarify the issue by focusing on workers involved in the manufacture of specific pesticides, but these studies have been generally negative (Blair et al. 1985). Other studies focusing on pesticide applicators, however, have found increased risks of brain cancer, thereby indicating that pesticides may be a culprit (Blair et al. 1985). Some pesticides contain alkyl ureas -- precursors of N-nitroso alkyl ureas, which are known to be powerful neurological carcinogens in animal studies (Musicco et al. 1988). N-nitroso compounds are discussed in more detail below. Other chemicals that cause brain tumors in rats include aryl dialkyltriazines, which are related to some common herbicides; and ethylene oxide, which is a registered pesticide commonly used to sterilize equipment in the health care industry and to fumigate materials in industrial settings.

Childhood Brain Tumors and Pesticides: A review of studies that looked at pesticides and childhood cancer found that nine of the 17 studies reported increased risk of brain cancer to be associated with pesticide exposure (Zahm and Ward 1998). Five additional studies found a positive relationship that was not strong enough to be reported as being statistically significant. Only three studies reported no excess risk associated with pesticide exposure. As in adulthood, living on a farm is associated with an increased risk of brain tumors. In particular, primitive neuroectodermal tumors (PNETs) are increased by 3.7-fold with farm residence prenatally, and 5-fold with farm residence in childhood (Yeni-Komshian and Holly 2000).

In Los Angeles, mothers of more than 224 children with brain cancer and a similar number of children without the disease were compared for a history of environmental exposures. Reported use of flea or tick products in the home was associated overall with a 70% increased risk of brain tumor. The risk was 2.5-fold among children less than five years of age. When the researchers asked specifically about sprays and foggers used for fleas and ticks, the risk was over 10-fold. This study reported a dose-response relationship, in which greater use of the products, or usage not according to the label, was associated with higher risks (Pogoda and Preston-Martin 1997). Another household pesticide linked to a five-fold increased risk of brain tumors is lindane, a chemical used to treat head lice and scabies (Davis et al. 1993). This same study found that children living in homes where “no-pest” strips were reported to have been used were five times more likely to develop brain tumors. These strips contain the volatile organophosphate insecticide dichlorvos, or DDVP. Reported use of flea collars on household pets also conferred a five-fold increased risk of childhood brain tumors. Because this study was small, it is considered

preliminary. An exploratory study reported that children diagnosed with brain tumors in the Baltimore area were more than twice as likely to have been exposed to insecticides during household exterminations than children without cancer (Gold and Gordis 1979; Gold et al. 1979). All of these studies must be interpreted with caution, as families of people affected by serious diseases are more likely to recall past exposures, whereas healthy people may forget to report exposures to substances such as household pesticides.

Parental work in agriculture or other pesticide-exposed occupations has been associated with brain tumors in children. A large study of children of farmers in Norway found that parents who used pesticides had a three-fold higher risk for having a child with certain types of brain tumors (Kristensen et al.1996). In France, living on a farm increased the risk of childhood brain tumor by 2.5-fold, and household use of pesticides conferred an increased risk of 80% (Cordier et al. 1994). Another European study looked at 260 children with brain cancer and similar children without the disease, and found that the risk of disease was higher for children whose parents worked in agriculture (Cordier et al. 1997). In California, a large geographically-based study using the state cancer registry and pesticide use reporting system generally found no associations between living in an area of high pesticide use and childhood cancer rates, including rates of brain cancer (Reynolds et al. 2002).

Solvents and Other Industrial Chemicals

Adult Brain Tumors and Industrial Chemicals: Several common industrial chemicals, including vinyl chloride and acrylonitrile, can cause brain tumors in laboratory rats. Vinyl chloride is the main building block of polyvinyl chloride (PVC) plastic, while acrylonitrile is used in the manufacture of numerous polymers and synthetic rubbers. Workers in the petrochemical industry and, specifically, in the production of polymers (such as PVC or acrylonitrile-based polymers), had an elevated risk of brain tumor (Beall et al. 2001). Numerous studies have shown elevated cancer risk among workers in the PVC industry and in the rubber industry, as well as in industries involved in the production of petroleum and petrochemicals (Brownson et al. 1990). A National Cancer Institute study reported associations between astrocytic brain cancer and occupational exposure to several solvents, including carbon tetrachloride, methylene chloride, tetrachloroethylene, and trichloroethylene. Solvents are a wide variety of petrochemicals commonly used in industry and in consumer products. The association with the common solvent methylene chloride (dichloromethane) was particularly strong and increased with intensity and duration of exposure (Heineman et al. 1994). Methylene chloride is found in many varnish removers, degreasers, and automotive products. One study in France reported an association between work with wood preservatives such as pentachlorophenol and gliomas. Although the initial increased risk reported in this study was 60%, the researchers subsequently identified additional cases of glioma in the wood preserving industry (Cordier et al. 1988).

Childhood Brain Tumors and Solvents: A large number of studies have consistently shown that children who develop brain tumors are more likely to have parents who report significant solvent exposure. The associations between solvents and brain tumors exist for both maternal and paternal occupational exposures, particularly during the period before the child is born. A study in California and Washington interviewed parents of 540 children with brain cancers and parents of more than 800 other children who were similar, but did not have the disease. The study found that children with brain cancer were more likely than other children to have had parents who worked in the chemical industry (McKean-Cowdin et al. 1998).

Children whose mothers work in jobs involving automotive vehicles, or whose jobs involve use of solvents may be at greater risk of brain tumors (Viel et al. 1998). A New York study focusing on childhood neuroblastoma found that risks were higher among children of mothers whose jobs involve exposure to solvents such as acetone or petroleum, or to lead or insecticides (Kerr et al. 2000). Paternal petroleum exposure also conferred a slightly increased risk in this study. In a different study, paternal exposure to diesel fuel, lacquer thinner, and turpentine, were all specifically associated with neuroblastoma in the child (DeRoos et al. 2001). Other studies have confirmed these results, indicating that exposure of either parent to solvents before the birth of the child increases the risk of a variety of brain tumors, including primitive neuroectodermal tumors, and astroglial tumors (Cordier et al. 1997).

Electomagnetic Fields and Cell Phones

Extremely low frequency electromagnetic fields (EMF), in the range of 50-60 Hz, are created from the generation, transmission, and use of electricity. EMF exposure occurs at high levels in certain occupations, and can also occur when people live near high tension powerlines, or during the use of some common household appliances such as electric blankets and hairdryers. The signal from a cellular telephone is radiofrequency radiation, a higher frequency type of EMF. There has been a large amount of research into the possible cancer-causing effects of EMF. Some studies have found links between exposure and brain tumors in both adults and children. Unfortunately, the research on EMF is fraught with difficulties, including the fact that exposure to EMF is ubiquitous, imperceptible, and comes from many sources that vary greatly over time and across short distances. EMF also consists of an enormous number of different frequencies of electrical and magnetic radiation fields, and it is not clear whether all of these have similar biological effects. Perhaps due to these problems, the research on brain tumors and EMF is very conflicting, and it remains unclear whether a link exists (Ahlbom et al. 2001).

Several studies have reported that paternal work in high-EMF industries, such as electrical work, increases risk of brain tumor in children (Cordier et al. 2001). One study in the U.S. and Canada, of 538 children with neuroblastoma, found that mothers of these children were nearly three-times more likely to report working in a job classified as exposed to EMF (DeRoos et al. 2001). Other studies have reported elevated risks of neuroblastoma in the range of 60-90% among children of fathers exposed to EMF at work (Wilkins and Hundley 1990). It is not clear how paternal exposure to EMF could possibly increase cancer risk in children, as EMF does not affect the

genes and residues cannot be transported home on shoes and clothing, so these results would require further research in an effort to identify a plausible way that male EMF exposure could affect offspring. In adults, most researchers have identified modestly increased risks of brain cancer, of borderline statistical significance, with increasing occupational exposure to EMF (Floderus et al. 1993).

Five major epidemiologic studies have examined potential associations between cell phone use and brain tumors. The first study included 233 brain cancer patients and 466 controls diagnosed between 1994-1996 in Sweden. This study found no increased risk overall, no risk of developing specific tumor types, no dose-response relationship. There was, however, a 2.4-fold increase in temporal lobe tumors on the same side that the user habitually placed the phone (Hardell et al. 1999). The subsequent year, another large study of 469 brain tumor patients and 422 controls was published. This study was done between 1994-1998 in New York, Providence, and Boston. There was no overall association between brain tumors and cell phones and no dose-response relationship. There was, however, a doubling of neuroepitheliomatous tumors and a marginally significant concordance with what side the phone was used on for cerebral hemisphere tumors, but not temporal lobe tumors (Muscat et al. 2000). An even larger study, of 782 brain cancer patients and 799 controls between 1994-1998 in Phoenix, Boston, Pittsburgh found absolutely no links between cell phone use and brain tumors, and in fact, found a nonsignificantly decreased risk overall and with neuroepitheliomatous tumors (Inskip et al. 2001). In 2002, a major Swedish study with 1429 cases and 1470 controls covering the years 1997-2000 revived the debate by finding an association between analogue cell phone use and a 30% increased risk of brain tumor. The risk climbed to 80% if the user had been using cell phones for more than ten years. The most significant association was with temporal lobe tumors on the same side that the phone was used, with an increased risk of 2.5-fold, and with acoustic neuromas (3.5-fold) (Hardell et al. 2002). There was no association with digital cell phones or cordless telephones. A huge cohort study looked at everyone in Denmark between 1982 and 1995 who was signed up as a subscriber with a cell phone company. These 420,000 people were cross-linked with the national cancer registry. This study did not show any excesses in brain cancers among the cell phone users compared to the rest of the population (Johansen et al. 2001). Studies in laboratory animals have failed to clarify the situation, and have also reported conflicting results. In summary, the cell phone data are confusing and conflicting, but there does not, at this time in the scientific literature, appear to be a dramatic or large association between cell phone use and brain tumors. On the other hand, several well-designed studies have identified some links, particularly with analogue phones. In addition, some of the earlier studies were likely done too soon after cell phones came into widespread use, meaning that most of the cell phone ‘users’ were not exposed very much or for very long. Because the latency period for brain tumors is unknown, the cell phone effect, if it exists, may begin to become clearer over time. Meanwhile, newer cell phones are more likely to use digital technology and are designed to emit less radiofrequency radiation.

Nitrites

N-nitroso alkyl ureas are known to cause brain tumors at relatively low doses in laboratory rats (Musicco et al. 1988). These tumors occur in rats fed sodium nitrite, which is used to cure meats such as hot dogs, bacon, and ham; in combination with ethylurea, a chemical that is related to some common pesticides. An epidemiological study of over 1300 mother-child pairs in the U.S., found that mothers of children with brain tumors were more likely to report a history of frequent consumption of processed meats (Preston-Martin et al. 1996). In fact, high consumption of processed meat conferred a doubling of risk of brain tumor. The risk appeared to be greater if the mother also did not take prenatal vitamins, whereas regular consumption of prenatal vitamins reduced the risk. This is consistent with the theory that anti-oxidant vitamins such as vitamin C and E might block the formation of nitroso compounds in the stomach. This study is consistent with a prior report that maternal hot dog consumption of one or more times per week was associated with a 2.3-fold increased risk of childhood brain tumor (Sarasua and Savitz 1994). A review of the fourteen studies to date on this topic concluded that the potential for recall bias, the relatively weak magnitude of the association, and the inconsistency between study findings make it difficult to evaluate whether or not there is a link between consumption of cured meat and childhood brain tumors (Blot et al. 1999).

Although the data are even more conflicting in adults, some studies have found associations between dietary consumption of N-nitroso dimethylamine (NDMA) – mainly from bacon and corned beef - and brain tumors, especially in men. Studies looking for links between nitrates in drinking water and brain tumor risk have been limited by indirect estimates of exposure and are mostly negative (Mueller et al. 2001). Although the scientific evidence on this issue is still preliminary, the link between nitrite exposure and brain tumor risk is worthy of additional research, and is an exposure that can be avoided.

Summary

In summary, brain tumors may be caused, at least partially, by environmental factors. Although living on a farm is clearly associated with an increased risk of this disease, it is not clear whether the causal factor is related to pesticides, microorganisms, petroleum products, or other farm exposures. Prenatal and childhood exposure to pesticides have been linked to brain tumors in a considerable number of studies, but in adults the evidence is less strong. The data on other factors, such as solvents, industrial chemicals, EMF, and cell phones are conflicting, and it is not clear to what degree these links are important in the disease. The epidemiologic research linking N-nitroso compounds in the diet to brain tumor is supported by animal evidence. Much more research into the environmental causes of brain tumors is needed to resolve the remaining questions.

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