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Epidemiology of Brain Tumors

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Brain cancer accounts for approximately 1.4% of all cancers and 2.3% of all cancer-related deaths. The tumors are particularly deleterious in that they can interfere with the normal brain function that is essential for life (American Cancer Society, 2000). The American Cancer Society estimated that 16,800 individuals would be diagnosed with malignant brain tumors in 1999 and that 13,100 of those individuals would die from their disease (American Cancer Society, 2000). Despite their high degree of lethality and inescapable traumatic impact, brain tumors rarely metastasize beyond the central nervous system (CNS).

Although there has been a recent increase in the number of epidemiologic studies of brain cancer, little consensus exists regarding the nature and magnitude of the risk factors contributing to its development. In addition to the differences in methods and eligibility criteria used and in the representativeness of the patients studied, other confounding factors exist. These include the variable use of proxies to report information about case subjects; differences of control groups selected; substantial heterogeneity of primary brain tumors; inconsistencies in histologic diagnoses, definitions and groupings; and difficulties inherent in retrospective analyses.

ETIOLOGY AND RISK FACTORS OF BRAIN TUMORS

Ionizing Radiation

There is reasonable consensus from ongoing research that therapeutic ionizing radiation is a strong risk factor for intracranial tumors (Bondy et al., 1994; Hodges et al., 1992). Even the comparatively low doses (averaging 1.5 Gy) used to treat ringworm of the scalp (tinea capitis) have been associated with relative risks of 18, 10, and 3 for nerve sheath tumors, meningiomas, and gliomas, respectively (Bondy et al., 1994; Hodges et al., 1992). Other studies showed a high (17%) prevalence of prior therapeutic radiation among patients with glioblastoma or glioma and increased risk of brain tumors in children after radiation for acute lymphoblastic leukemia.

Diagnostic radiation, on the other hand, does not seem to play a role in glioma; three case–control studies of exposure to dental X-rays reported relative risks of 0.4, 1.2, and 3.0. The evidence is slightly stronger for meningioma, for which three of four studies have shown relative risks exceeding 2 after exposure to dental X-rays. Because the studies with positive findings were all conducted in Los Angeles (Hodges et al., 1992), they should be replicated in other geographic areas to test the validity of existing data.

The role of prenatal exposure to radiation in the etiology of childhood brain tumors is unclear. Japanese studies of individuals exposed in utero to atomic bomb radiation revealed no increased incidence of brain tumors (Hodges et al., 1992). Other studies that reported increased relative risks of 1.2 to 1.6 for those exposed prenatally were statistically insignificant because of their small sample sizes. Furthermore, relative risks of this low magnitude associated with a comparatively uncommon exposure cannot account for most childhood brain tumors. Parental ex-

posure to ionizing radiation before conception of the affected child has not been shown to be a risk factor for childhood brain tumors (Hodges et al., 1992).

Occupational risk findings from atomic energy and airline employees are equivocal. A small but statistically significant elevated risk of 1.2 for the occurrence of brain tumors in nuclear facility employees and nuclear materials production workers has been reported (Hodges et al., 1992; Loomis and Wolf, 1996). However, the confounding effect modification by chemical exposures complicates interpretation of causality. One study reported increased mortality from brain tumors among airline pilots, possibly implicating exposure to cosmic radiation at high altitudes in brain tumor risk. Conversely, another study of airline pilots found no excess of brain tumor deaths (Bondy et al., 1994), a finding substantiated by a more recent population-based cohort study, which demonstrated that although malignant melanoma and skin cancer were found in excess in cockpit crew members with a long flying history, there was no increased risk of brain cancer in pilots (Gundestrup and Storm, 1999).

Electromagnetic Fields

The debate on the impact of electromagnetic fields on brain cancer continues despite largely negative findings, and it has been prolonged by methodologic difficulties with some study designs. Wertheimer and Leeper (1979) first reported an increased risk of cancer and later (1987), an increased risk of brain tumors and leukemia in children living in homes in Denver near high-current versus low-current wiring. This report triggered widespread public and scientific interest in the potential health effects caused by electromagnetic fields. One meta-analysis revealed a 50% increased risk of childhood brain tumors in children living in high versus low wire-coded homes (Meinert and Michaelis, 1996). In a meta-analysis of 29 studies of adult brain tumors related to occupational exposures to electric and magnetic fields, Kheifets and colleagues (1995) found a significantly (10% to 20%) increased risk for brain cancer among electrical workers but found no evidence for a consistent dose–response relationship between disease and jobs considered to have higher versus lower exposures.

A recent case–cohort analysis of brain cancer and leukemia in electric utility workers found that magnetic field exposure remained unrelated to leukemia mortality but was positively associated with brain cancer mortality on the basis of both cumulative and average magnetic field indices gathered from a refined magnetic field job-exposure matrix. Increased risk of brain cancer was found in relation to career exposure, with risk ratios of 1.8 (95% CI = 0.7–4.7) and 2.5 (95% CI = 1.0–6.3) in the uppermost categories for cumulative and average exposure, strongest for exposure 2 to 10 years past (Savitz et al., 2000). Another epidemiologic study of adult brain tumors (reviewed by Wrensch et al., 2000) and a recent large population-based study of adult glioma in the San Francisco Bay area provided no strong support for the hypothesis that high electromagnetic fields in homes may increase the risk of brain tumors (Wrensch et al., 1999). In the San Francisco study, 492 adults with glioma and 463 controls were equally likely to have lived in homes with high wire-codes during the 7 years before diagnosis. Spot measurements taken in homes also showed no correlation with controls (Wrensch et al., 1999).

Although a recent study found that exposure to 60 Hz magnetic fields stimulated proliferation of human astrocytoma cells in vitro (Wei et al., 2000), a study of childhood brain tumors and residential electromagnetic fields by Kheifets et al. (1999) found no support for an overall association between electromagnetic fields and childhood brain cancer. This lack of support applied to all surrogates of past magnetic fields, including wire code, distance, measured or calculated fields, and use of appliances by either child or mother. Mutnik and Muscat (1997) in a case–control study similarly found no increased risk of brain cancer with exposure to the use of common household appliances, including personal computers, electric heaters, electric hair dryers, and electric razors. The difficulty with many of the studies in this area, diverse as they are, is that conclusions may have been based on a sample size insufficient to detect small, elevated risks, skewing their results. Furthermore, most epidemiologic studies do not present quantitative exposure or data on the specific frequencies of electromagnetic fields (Blettner and Schlehofer, 1999).

The fact that measurements of electromagnetic fields are not precise also confounds interpretation of existing data. Wire codes of electrical distribution to homes and spot measurements of electromagnetic fields in and around homes can lead to incorrect ex-

posure estimates (EMF Science Review Symposium, 1998). Wire codes also do not reflect exposures from internal wiring or household appliances. Spot measurements change over time and do not reflect the actual measurement in homes. Furthermore, the spot measurements may be made in places where the occupants spend little or no time. Such assessments also neglect exposures outside the home, which may exceed those in the home.

A positive Swedish study of adult leukemia and CNS tumors found increased risks in those exposed both residentially and occupationally, but not in those with no exposure or with only residential or only occupational exposure (EMF Science Review Symposium, 1998). The Swedish study was able to calculate residential magnetic field exposures over time because of detailed information available from Swedish power suppliers. Such data are not available in United States (Floderus et al., 1994). Finally, McKean-Cowdin et al. (1998) found that children of fathers employed as electrical workers were at increased risk of developing brain tumors of any histologic type (OR, 2.3; 95% CI, 1.3–4.0).

Aside from the lack of precise information about total electromagnetic field exposure and its duration, an even more basic limitation in assessing relative risk has been the failure, thus far, to show that electromagnetic fields induce mutations, which in turn might promote tumorigenesis and the development of brain tumors (Gurney and van Wijnagaarden, 1999).

Cellular Telephones

The use of cellular telephones has grown remarkably over the last decade, and it is estimated that more than 500 million individuals worldwide use hand-held cellular devices. The telephones contain a small transmitter that emits low-energy radio frequency radiation next to the head. This led to public concern that individuals exposed to radiation emitted from wireless communication technologies might have an increased risk of developing tumors of the brain and nervous system. To date, six papers have been published (Rothman et al., 1996; Dreyer et al., 1999; Hardell et al., 1999; Muscat et al., 2000; Inskip et al., 2001; Johansen et al., 2001), and none of the studies supports an association between use of these telephones and tumors of the brain or other cancers.

The first study by Rothman and colleagues (1996) reviewed mortality among more than 250,000 customers of a large cellular phone operator in the United States and did not find an increased risk after follow up of only 1 year. The numbers of brain cancers (n = 6) and of leukemias (n = 15) were small, and there were no statistically significant associations with number of minutes of phone use per day or years of phone ownership found in a study 3 years later (Dreyer et al., 1999). The third study, a case–control study from Sweden by Hardell and colleagues (1999), reported a statistically nonsignificant increased risk for brain tumors on the side of the head on which cellular telephones were used. However, the risk for brain tumors overall was not increased, and there were methodologic concerns related to ascertainment of cases. The fourth report was a case–control study from five academic institutions in the United States that reported 469 patients with primary brain cancer and 422 matched controls between 18 and 80 years of age (Muscat et al., 2000). They found no association with brain cancer by duration of use (p = 0.54) and an inconsistent association with side of the head where cellular telephones had been used that led them to conclude that it "is not associated with risk of brain cancer." The fifth study was a hospital-based case– control study conducted by investigators at the National Cancer Institute (Inskip et al., 2001). They included 782 patients and 799 controls. The relative risks associated with cellular phone use for more than 100 hours was 0.9 for gliomas (95% CI, 0.5–1.6), 0.7 for meningioma (95% CI, 0.3–1.7), and 1.4 for acoustic neuroma (95% CI, 0.6–3.0). There was no evidence of higher risks among persons who used cellular phones for more than 5 years or of more tumors on the side of the head where the phone was typically used.

The sixth study was a retrospective cohort study of cancer incidence conducted in Denmark using subscriber lists from the two Danish operating companies (Johansen et al., 2001). Investigators identified 420,095 cellular telephone users during the period from 1982 through 1995 and linked the list with the Danish Cancer Registry. They observed 3391 cancers overall and expected 3825 cases (SIR, 0.89; 95% CI, = 0.86–0.92), and the risk of cancers of the brain or nervous system was also lower than expected (SIR, 0.95; 95% CI, 0.81–1.12).

In addition, a large occupational cohort mortality study among 195,775 employees of Motorola, a manufacturer of wireless communication products, did not support an association between occupational ra-

dio frequency exposure and brain cancers or lymphoma/leukemia (Morgan et al., 2000).

To date, the studies all seem to support the hypothesis that there is no association between use of these telephones and tumors of the brain or other cancers.

FOOD AND DIETARY FACTORS

Several observations have led to studies of diet and brain tumors. In experimental animal studies, N-nitroso compounds have been clearly identified as neurocarcinogens (Koestner et al., 1972; Swenberg et al., 1975a,b; Preston-Martin, 1988). Other investigations have identified several mechanisms involving DNA damage through which N-nitroso compounds might cause brain tumors (Kleihues et al., 1979; Magnani et al., 1994; Bondy et al., 1994). N-nitroso compounds can initiate carcinogenesis in the CNS through both prenatal and postnatal exposure, with more tumors in animals resulting from fetal rather than postnatal exposures (Koestner et al., 1972; Swenberg et al., 1975a,b). Because there is a substantial lag between exposure and tumor formation it is likely that childhood exposure produces tumors in adults. Animal studies have shown that a wide variety of primates and other mammals are susceptible to chemically induced brain tumors (Preston-Martin, 1988).

For humans, the ubiquity of N-nitroso compounds has complicated their epidemiologic evaluation as carcinogens. About one-half of all human exposures in the digestive system occur when common amino compounds produced from fish, other foods, and drugs contact a nitrosating agent (such as nitrites in cured meats) in the right enzymatic milieu (Magnani et al., 1994). Equally common external exposures include agents such as tobacco smoke, cosmetics, auto interiors, and cured meats. Complicating matters further, some vegetables convert nitrates to nitrites but also contain a high enough level of vitamins to block formation of N-nitroso compounds. A meaningful assessment of risks from exposure to dietary and environmental compounds is thus difficult to achieve. Nevertheless, many studies have tried to examine major dietary sources of these chemicals and assess safeguards against formation of nitrosoureas presented by vitamins such as C and E, which are thought to inhibit N-nitroso formation.

There has been no consensus arising from the plethora of human studies. Diet and vitamin supplementation investigations have provided only limited support for the hypothesis that dietary N-nitroso compounds increase the risk of both childhood and adult brain tumors (Magnani et al., 1994; Berleur and Cordier, 1995). However, a verbal history of higher levels of consumption of foods cured with nitrosamines have been reported among brain tumor patients and mothers of brain tumor patients compared with control observers (Preston-Martin et al., 1996; Preston-Martin and Mack, 1996). Also, lower rates of N-nitroso compound formation after increased consumption of fruits and vegetables and vitamins that might block nitrosation or harmful effects of nitrosamines has been observed in some, but not all, studies.

Preston-Martin et al. (1998) uncovered a possible reduction in risk for pediatric brain tumors from maternal vitamin use during pregnancy. Their international case–control study examined data from 1051 cases and 1919 controls in eight geographic areas of Europe, Israel, and North America. Despite a huge international variation in the use of supplements by controls, combined results suggest that maternal supplementation for two trimesters may decrease the risk of brain tumor, with the greatest risk reduction among children diagnosed under 5 years of age whose mothers used supplements during all three trimesters of pregnancy.

Lee et al. (1997) found that adults with glioma were more likely than controls to consume diets high in cured foods and nitrites and low in fruits and vegetables rich in vitamin C. The effect was more pronounced in and only achieved statistical significance in men. Although this finding is compatible with the hypothesis that N-nitroso compounds might play a role in human neuro-oncogenesis, the observed patterns also support the hypothesis of nuclear and mitochondrial DNA damage caused by an increased level of N-nitroso compounds and the consequential oxidative burden versus antioxidant protection.

One comprehensive survey of nitrosamines in food and beverages found that beer contaminated with the nitrosamine derivative NDMA proved harmful, especially in Germany. The source of the contamination was traced to oxidation of malt (Mangino et al., 1982). Beer in several countries produced a major source of exposure to carcinogenic nitrosamines because of the very large quantities consumed. NDMA

was also present in alcoholic beverages of various kinds, but at lower concentrations than in beer, therefore creating a lower cancer risk probably because of the smaller amounts consumed relative to beer. Despite much investigation, particularly in connection with pediatric brain tumors, alcoholic products have not been implicated as causing brain tumors (Wrensch et al., 1993).

Because tobacco smoke contains polycyclic aromatic hydrocarbons and nitroso compounds, many studies have attempted to establish a relationship between brain tumors and cigarette smoke. No significant effect has been found from smoking, although two studies report increased risk of adult glioma from smoking unfiltered, but not filtered, cigarettes (reviewed by Wrensch et al., 1993; Lee et al., 1997). A suspected role of secondary, or passive, smoke has more empirical support. Several studies found slightly increased relative risks, generally smaller than an order of magnitude associated with recognized hazards of exposure to passive smoking (1.2 to 1.3 for adult lung cancer and cardiovascular diseases) (Scheidt, 1997; Schwarz and Schmeiser-Rieder, 1996). Tumors most often associated with maternal smoking in pregnancy and passive smoke exposures are childhood brain tumors and leukemia/lymphoma, with risks as high as or greater than 2 in selected studies (Cordier et al., 1994; Filippini et al., 1994; Sasco and Vainio, 1999). Several studies have found elevated risk more closely associated with paternal rather than maternal smoking (Magnani et al., 1989).

INDUSTRY AND OCCUPATION

Attempts to link specific chemicals with human brain tumors in occupationally or industrially exposed groups have proved inconclusive. Thomas and Waxweiler (1986) published a comprehensive review of occupational risk factors for brain tumors and established a group of suspect chemicals and occupations. Additional studies in the intervening 14 years have not established a conclusive link between any of these factors and brain tumor risk. Many occupational and industrial studies focused on individuals exposed to carcinogenic and neurotoxic substances, including organic solvents, lubricating oils, acrylonitrile, formaldehyde, polycyclic aromatic hydrocarbons, phenols, and phenolic compounds, all of which are components of workplace exposures and induce brain tumors in experimental animals. Animal CNS carcinogenicity studies, mainly in rats, have shown that susceptibility is significantly influenced by strain, gestational age, and fetal versus adult status, factors that cannot be accounted for in or generalized to human occupational cohort exposure studies.

Animal studies assess exposures that cannot be tested in humans. For instance, some compounds such as polycyclic aromatic hydrocarbons generally induce brain tumors only through direct placental implantation, not through inhalation or dermal exposure as in worker populations. Workers are also rarely exposed to a single chemical but are exposed to many chemicals that probably interact to affect risk. Follow-up studies of occupationally induced brain cancer usually consist of too few affected subjects to permit pinpointing the causal chemicals, physical agents, work processes, interactions, or mechanisms involved.

There have been interesting occupational findings relating to motor vehicle operation with an associated increased risk for developing brain tumors. Kaplan et al. (1997) assessed occupationally related risk factors in a population-based, case–control study of 139 patients with primary brain tumors carried out in central Israel between 1987 and 1991. For each case, two control groups were matched by age (± 5 years), sex, and ethnic origin. Odds ratios for brain tumors showed a significantly increased risk among blue-collar workers, especially among those employed in the textile industry, and among drivers and motor vehicle operators. When tumor types were assessed separately, a significantly increased risk for malignant brain tumors was found among drivers and motor vehicle operator occupations, whereas for meningiomas there was an increased risk among weavers and tailors.

Other studies suggest that certain parental occupational exposures might be harmful to children (Cordier et al., 1997; Colt and Blair 1998). Data suggest that childhood nervous system tumors are increased if parents worked with solvents, polycyclic aromatic hydrocarbons, paints, and/or were employed in motor vehicle-related occupations. Results from a study by Cocco et al. (1998) to determine the risk of brain cancer and occupational exposure to lead lend some support to the hypothesis of an association between parental occupational exposure to lead and brain cancer risk in their children.

No definitive link has, however, been established between brain tumors and specific chemicals or

strongly suspected carcinogens. Organochlorides, alkyl ureas, and copper sulfate compounds reliably induce cancer in laboratory animals, for example. Yet studies of agricultural workers using these chemicals have equally as often produced negative and positive findings with regard to brain tumor risk. Nor have all studies shown excess risk for workers involved in manufacturing pesticides or fertilizers. On the other hand, four of five studies of pesticide applicators found a nearly threefold elevated risk of developing brain tumors (Khuder et al., 1998). Viel et al. (1998) assessed the association between vineyard pesticides and brain cancer mortality among agricultural workers. A pesticide exposure index in vineyards was calculated for 89 French geographical units (1984 to 1986). Mortality from brain cancer among these farmers was significantly higher than mortality for the overall population. Univariate and multivariate analyses revealed a significant association between pesticide exposure in vineyards and brain cancer.

Daniels et al. (1997) critically reviewed 31 epidemiologic studies published between 1970 and 1996 to determine whether occupational or residential exposure to pesticides by either parents or children was related to increased risk of childhood cancer. The reported relative risk estimates were generally modest, although the highest risk estimates were found in those studies where pesticide exposure was measured in more detail. Frequent occupational exposure to pesticides or home pesticide use was more strongly associated with childhood leukemia and brain cancer than either professional exterminations or the use of garden pesticides. Occupational pesticide exposure was also associated with increased risk of Wilm's tumor, Ewing's sarcoma, and germ cell tumors. Residence on a farm, a proxy for pesticide exposure, was associated with increased risk of a number of childhood cancers. However, as in studies dealing with electromagnetic fields, methodologic limitations to many studies restrict the value of their conclusions. These limitations include indirect exposure classification, small sample size, and potential biases in control selection.

In a follow up of a population-based case–control study of pediatric brain tumors in Los Angeles County, California, involving mothers of 224 cases and 218 controls, Pogoda and Preston-Martin (1997) investigated the risk of household pesticide use from pregnancy to diagnosis. Particularly in subjects younger than 5 years of age, risk was significantly elevated for prenatal exposure to flea/tick pesticides (OR, 1.7; 95% CI, 1.1–2.6). Prenatal risk was highest for mothers who prepared, applied, or cleaned up tick/flea products themselves (OR, 2.2; CI, 1.1–4.2). A significant trend of increased risk with increased exposure was observed for number of pets treated ($p = 0.04$). Multivariate analysis of types of flea/tick products indicated that sprays/foggers were the only products significantly related to risk (OR, 10.8; CI, 1.3–89.1). Elevated risks were not observed for termite or lice treatments, pesticides for nuisance pests, or yard and garden insecticides, herbicides, fungicides, or snail killer. The findings indicate that chemicals used in flea/tick products may increase the risk of pediatric brain tumors and suggest that further research is warranted to determine the specific chemicals causing the most risk.

Kristensen et al. (1996) looked at the possible connections between parents working in agriculture in Norway and cancer in their children. Factors linked to horticulture and the use of pesticides are associated with cancer at an early age, whereas factors in animal husbandry, in particular poultry farming, are associated with cancers in later childhood and young adulthood. Risk factors were found for brain tumors, in particular nonastrocytic neuroepithelial tumors; for all ages pig farming tripled the risk. Indicators of pesticide use had an independent effect of the same magnitude in a dose–response fashion, strongest in children aged 0 to 14 years. Horticulture and pesticide indicators were associated with all cancers at ages 4 to 9 years, Wilm's tumor, non-Hodgkin's lymphoma, eye cancer, and neuroblastoma. Chicken farming was associated with common cancers of adolescence and was strongest for osteosarcoma and the mixed cellular type of Hodgkin's disease. The crude exposure indicators available limit this large cohort study, with the resulting misclassification likely to bias any true association toward unity.

Yeni-Komshian and Holly (2000) reviewed data from seven case–control studies published between 1979 and 1998 that considered a possible relationship between fetal or childhood exposure to farm animals or pets and childhood brain tumors. Five of the seven studies examined childhood residence or exposure of mother or child to farm animals or pets and childhood brain tumors. Four of these five studies reported elevated risk for childhood brain tumors with ORs ranging from 0.9 to 2.5 for maternal exposures and from 0.6 to 6.7 for children's exposures.

Later and larger studies subsequently examined histologic type and reported excess risk for primitive neuroectodermal tumors with farm residence prenatally (OR, 3.7; CI, 0.8–24) or in childhood (OR, 5.0; CI, 1.1–4.7). Increased risk of primitive neuroectodermal tumors was also associated with maternal exposure to pigs or poultry.

Because they involve production of many suspect carcinogens, synthetic rubber production and processing have received careful scrutiny by investigators who found a median increase in the occurrence of brain tumors of as much as 90% (Thomas and Waxweiler, 1986; Bohnen and Kurland, 1995). The by-products of synthetic rubber processing, such as coal tars, carbon tetrachloride, N-nitroso compounds, and carbon disulfide, might appear to account for the increased risk. In contrast, other studies showed no increased risk (Symons et al., 1982), or a decreased risk, of brain tumors caused by working in this industry, but studies have usually failed to show a link with a single chemical.

An association seems to exist between exposure to vinyl chloride and brain tumors. Vinyl chloride has been shown to induce brain tumors in rats, and 9 of 11 studies of polyvinyl chloride production workers have shown a median increased relative risk of dying of brain tumors that is twofold more than in the general population. A large European multicenter cohort study investigating the dose–response relationship between vinyl chloride and liver cancer, as well as assessing cancer risk for other sites, found no particular link between brain cancer and exposure (Simonato et al., 1991). Some argue, however, that the small number of brain tumor cases and statistical insignificance shown by most research cast doubt on the existence of any causal relationship (McLaughlin and Lipworth, 1999; Kielhorn et al., 2000). Another problem with the overall meaningfulness of results has been that, in general, epidemiologic studies have not followed individuals over a period of time adequate for cancer to become clinically manifest (Kalmaz and Kalmaz, 1984).

Formaldehyde is an additional long-suspected compound. The numbers derived from experimental data and retrospective review are greater than for other chemicals, but the conclusions are just as elusive. Formaldehyde produces cancer in laboratory animals, and nearly 2 million workers in the United States are occupationally exposed to it. Thirty epidemiologic studies of segments of this large group were evaluated by Blair and colleagues (1990). The unclear result was that elevated risk (approximately 50%) existed for those exposed in professional roles such as embalmers, pathologists, and anatomists. However, Blair et al. (1990) did not find a similar risk for industrial workers with formaldehyde exposure and therefore rejected a causal relationship between formaldehyde and human brain tumorigenesis. Other unknown cofactors may obscure the true risk in industrially exposed workers and create a skewed estimate of risk in associated occupational groups.

VIRUSES

Specific viruses, like chemicals, have been found to induce brain tumors in animal studies. As in the chemical studies, small numbers and negative findings hinder epidemiologic evaluation and conclusions. Performing aggressive studies of the role of viruses (and other infectious agents), in causing human brain tumors has been promulgated (Wrensch et al., 1993; Berleur and Cordier, 1995). The putative cancer–virus connection has been supported by several studies of animal tumor induction caused by viral exposure. Unfortunately, few epidemiologic studies have addressed the virus–tumor relationship probably because of the difficulties implicit in designing meaningful studies.

Between 1955 and 1963, 92 million U.S. residents received a Salk polio vaccine that may have been contaminated with simian virus 40 (SV40) (Shah, 1998). Levels of SV40 varied between lots and manufacturers. The vaccine was treated with formalin, but because SV40 is less susceptible to formalin inactivation than is poliovirus, the polio vaccine contained infectious SV40. Early cohort studies of cancer in SV40-contaminated poliovirus vaccine recipients demonstrated no clear association between SV40 exposure and cancer mortality among children in the United States (Fraumeni et al., 1970; Heinonen et al., 1973; Mortimer et al., 1981) and in Germany (Geissler, 1990). A recently published cohort study specifically examined the risk of ependymoma, osteosarcoma, and mesothelioma among Americans who as children received SV40-contaminated poliovirus vaccine (Strickler et al., 1999). There was no association between exposure and significantly increased rates of brain cancers, osteosarcomas, mesotheliomas, or medulloblastomas (Strickler et al.,

1999). Another study, one of the rare case–control studies of SV40 and cancer, showed no association with poliovirus immunization and childhood cancer among children in England, whereas yet another study showed a small association between poliovirus immunization and cancer in Australian children (Innis, 1968). Studies of maternal vaccination with SV40-contaminated vaccines have demonstrated an association with brain cancers in particular (Farwell et al., 1979; Heinonen et al., 1973). Interpreting these reports is difficult because of the small number of available cases and methodologic limitations. As with other brain tumor investigations, studies of SV40 are often case reports and follow ups, offering hints, clues, or perhaps merely coincidences that must be further tested and analyzed before any firm conclusions can be made.

Another virus investigated in a small number of studies is the human neurotropic polyomavirus JC virus, which is commonly excreted in urine, particularly by immunosuppressed, immunodeficient, and pregnant women. Khalili et al. (1999) recently detected JC virus in paraffin-embedded tissues from children with medulloblastoma. JC virus was also found in a rare case of pleomorphic xanthoastrocytoma (Martin et al., 1985) and in oligodendrogliomas (Rencic et al., 1996). However, JC virus exists in cancer-free subjects, and its connection, if any, to tumorigenesis is hypothetical at best.

Similarly, contradicting studies have found that more mothers of children with medulloblastoma than mothers of children without it were exposed to chicken pox, a herpes virus, during pregnancy. Wrensch and colleagues (1997b) found that adults with glioma in the San Francisco Bay area were significantly less likely to report having had either chicken pox or shingles than controls were. This observation was supported by serologic evidence that cases were less likely than controls to have antibody to varicella zoster virus, the agent that causes chicken pox and shingles. It is plausible that viruses and infectious agents explain the occurrence of brain tumors. However, as intriguing as this hypothesis is, further research is needed to clarify the role of viruses and any associations they may have with brain tumors. Linos et al. (1998) examined the hypothesis that exposure to influenza in pregnancy increased the risk of tumor in childhood. Ninety-four patients (ages $\leq$17 years) diagnosed in Greece with brain tumors or neuroblastomas from 1982 to 1993 were contrasted with 210 controls. The results show a significant association between influenza in pregnant women and occurrence of tumor in their children.

DRUGS AND MEDICATIONS

Few studies have examined the effects of medications and drugs on risk of adult brain tumors. A nonsignificant protective association was observed for headache, sleep, and pain medications (reviewed by Preston-Martin and Mack, 1996). Ryan and colleagues (1992) found that diuretics have a nonsignificant protective association with meningioma but have an opposite association with adult glioma, and they found essentially no association between antihistamine use and adult glioma, but a 60% increased relative risk for meningioma. Three studies have assessed childhood brain tumors and prenatal exposures to some or all of the following drugs: fertility drugs, oral contraceptives, sleeping pills or tranquilizers, pain medications, antihistamines, and diuretics. These studies have yielded few significant findings. Prenatal exposure to diuretics was 50% less common among children with brain tumors compared with controls in two studies but twice as common in one study. Prenatal exposure to barbiturates has not been consistently or convincingly linked with childhood brain tumors. Because nonsteroidal anti-inflammatory drugs are protective against certain cancers, the role of these drugs in inducing brain tumors, alone or with other factors, should be investigated.

SUSCEPTIBILITY TO BRAIN TUMORS

The most generally accepted current model of carcinogenesis is that cancers develop through an accumulation of genetic alterations that allow cells to grow out of the control of normal regulatory mechanisms and escape destruction by the immune system. Some inherited alterations in crucial cell cycle control genes, such as *P53,* as well as chemical, physical, and biologic agents that damage DNA, are therefore considered candidate carcinogens. Although rapid advances in molecular biology, genetics, and virology promise to help elucidate the molecular mechanisms behind the formation of human brain tumors, continued epidemiologic work is necessary to clarify the

relative roles of different mechanisms in that process. Genetic and familial factors implicated in brain tumors have been the subject of many studies and were previously reviewed by Bondy et al. (1994).

Familial Aggregation

Because only a small proportion of brain tumors are heritable, most are likely due to an interaction between genes and the environment. Whereas findings of familial cancer aggregation may suggest a genetic etiology, such aggregations may be the result of common familial exposure to environmental agents. Some epidemiologic studies have compared family medical histories of patients with brain tumor with those of controls. Significantly increased family histories, of both brain tumors and other cancers, have been reported. Although few studies have been published, a family history of brain tumors was associated with a relative risk ranging from 1 to 9 (Bondy et al., 1994). Differences in study methodologies, sample size, which relatives are included, how cancers were ascertained and validated, and the country where the study was conducted might explain some of the disparities among the findings.

Supporting a genetic etiology for brain tumors are studies of siblings reporting a high frequency of brain tumors between them, although twin studies have not demonstrated a similar association. In a family study of 250 children with brain tumors, Bondy et al. (1994) showed by segregation analysis a low probability that familial aggregation supported multifactorial inheritance rather than chance alone. Segregation analyses of the families of more than 600 adults with glioma revealed that a polygenic environment–interactive model best explained the pattern of occurrence of brain tumors (de Andrade et al., 2001). Given the previously described complexities of environmental impact and multiplicity of possible heritable factors, more work is required to delineate the manner by which genetic susceptibility affects brain cancer risk.

Hereditary Syndromes

A few rare mutated genes and chromosomal abnormalities can greatly increase one's chance of developing brain tumors. Numerous case reports have associated CNS tumors, including medulloblastoma, and gross malformations with gastrointestinal and genitourinary system abnormalities. Ependymoma has been associated with multisystem abnormalities; astrocytoma with arteriovenous malformation of the overlying meninges; and glioblastoma multiforme with adjacent arteriovenous angiomatous malformation and pulmonary arteriovenous fistula. Central nervous system tumors may also be associated with Down's syndrome, which involves chromosome 21. Three epidemiologic studies have found that patients with brain tumor are two to five times more likely than controls to have a mentally retarded relative, although the result was statistically significant in only one study (reviewed by Bondy et al., 1994). The heritability of brain tumors is also suggested by many reports of individuals with hereditary syndromes such as tuberous sclerosis, neurofibromatosis types 1 and 2, nevoid basal cell carcinoma syndrome, and syndromes involving adenomatous polyps, developing tumors (reviewed by Bondy et al., 1994).

Although there is convincing evidence that genetics plays a role in most cancers, including brain tumors, inherited predisposition to brain tumors probably accounts for only a very small percentage (5% to 10%) of them (Narod et al., 1991). In a review of 16,564 cases of childhood cancers diagnosed between 1971 to 1983 and reported to the National Registry of Childhood Tumors in Great Britain, Narod et al. (1991) estimated that the heritable fraction of childhood brain tumors was about 2%. In a population-based study of nearly 500 adults with glioma, only 4 individuals (less than 1%), all of whom were diagnosed in their thirties, reported having a known heritable syndrome (3 had neurofibromatosis and 1 had tuberous sclerosis) (Wrensch et al., 1997a).

Another class of heritable conditions are the cancer family syndromes (such as the Li-Fraumeni syndrome [LFS]), so-called because individuals in affected families have an increased risk of developing certain types of cancers. Individuals with LFS have inherited at least one copy of a defective gene. In LFS, cancers that develop include brain tumors, sarcomas, breast cancer, and cancer of the adrenal gland.

In some families, LFS has been linked to a gene mutation in *P53* on chromosome 17p (Bondy et al., 1994). In addition, germline *P53* mutations were found to be more frequent in patients with multifocal glioma, glioma and another primary malignancy, and a family history of cancer. In a population-based study of malignant glioma, Li et al. (1998) reported that *P53* mutation-positive patients were more likely than normally to have a first-degree relative affected with cancer (58% versus 42%) or personal history of a previous cancer (17% versus 8%). Further re-

search is necessary to determine the role of heredity, the frequency of *P53* mutations, and whether specific *P53* mutations correlate with specific exposures.

Metabolic Susceptibility

Genetic traits involved in susceptibility are common genetic alterations that influence oxidative metabolism, carcinogen detoxification, and DNA damage and repair. The role of genetic polymorphisms (alternative alleles) of genes established in the population in modulating susceptibility to carcinogenic exposures has been explored in some detail for tobacco-related neoplasms but much less so for other neoplasms, including gliomas. Due to rapid developments in genetic technology, an increasing number of potentially relevant polymorphisms are available for epidemiologic evaluation, including genes involved in carcinogen detoxification, oxidative metabolism, and DNA repair. The first study to report the role of metabolic polymorphisms in brain tumor risk found that the variants of cytochrome P450 2D6 *(CYP2D6)* and glutathione transferase *(GSTT1)* were significantly associated with increased risk of brain tumors (Elexpuru-Camiruaga et al., 1995). Kelsey et al. (1997) were unable to find an association between adult onset glioma with the *GSTT1*-null genotype or homozygosity for the *CYP2D6* variant, a poor-metabolizer genotype. However, when they stratified their data by histologic subtype, there was a significantly (threefold) increased risk for oligodendroglioma associated with the G*STT1*-null genotype. Trizna et al. (1998) found no statistically significant associations between the null genotypes of glutathione transferase-μ, *GSTT1,* and *CYP1A1* and risk of adult gliomas. However, they observed an intriguing pattern with *N*-acetyltransferase acetylation status, with a nearly twofold increased risk for rapid acetylation, but a 30% increased risk for intermediate acetylation.

It is unlikely that any single polymorphism is predictive of brain tumor risk. Therefore, a panel of relevant markers integrated with epidemiologic data should be assessed in a large number of study participants to clarify the relationship between genetic polymorphisms and brain tumor risk.

Mutagen Sensitivity

Cytogenetic assays of peripheral blood lymphocytes have been used extensively to determine response to genotoxic agents. The basis for these cytogenetic assays is that genetic damage is reflected by critical events in carcinogenesis in the affected tissue. To test this hypothesis, Hsu et al. (1989) developed a mutagen sensitivity assay in which the frequency of in vitro bleomycin-induced breaks in short-term lymphocyte cultures is used to measure genetic susceptibility. Bondy et al. (1996) modified the assay by using gamma radiation to induce chromosome breaks because radiation is a risk factor for brain tumors and can produce double-stranded DNA breaks and mutations. It is believed that mutagen sensitivity indirectly assesses the effectiveness of one or more DNA repair mechanisms. The following observations support this hypothesis. First, the relationship between chromosome instability syndromes and cancer susceptibility is well established (Busch, 1994). Patients with these syndromes also have defective DNA repair systems (Wei et al., 1996). Furthermore, patients with ataxia telangiectasia, who are extremely sensitive to the clastogenic effects of x-irradiation and bleomycin, differ from normal people in the speed with which aberrations induced by these agents are repaired, but not in the number of aberrations produced (Hittelman and Sen, 1988).

Gamma radiation-induced mutagen sensitivity is one of the few significant independent risk factors for brain tumors (Bondy et al., 1996). DNA repair capability and predisposition to cancer are hallmarks of rare chromosome instability syndromes and are related to differences in radiosensitivity. One in vitro study showed that individuals vary in lymphocyte radiosensitivity, which correlates with DNA repair capacity (Bondy et al., 1996). Therefore, it is biologically plausible that increased sensitivity to gamma radiation results in increased risk of developing brain tumors because of a genetic inability to repair radiation damage. However, this finding needs to be tested in a larger study to determine the roles of mutagen sensitivity and radiation exposure in the risk of developing gliomas. A positive mutagen sensitivity assay has been shown to be an independent risk factor for other cancers, including head and neck and lung, suggesting that the phenotype is constitutional (Cloos et al., 1996). The chromosome breaks are not affected by smoking or dietary factors (micronutrients) (Spitz et al., 1997).

Chromosome Instability

A number of chromosomal loci have been reported to play a role in brain tumorigenesis because of the

numerous gains and losses observed in those loci. For example, Bigner et al. (1988), reported gain of chromosome 7 and loss of chromosome 10 in malignant gliomas and structural abnormalities involving chromosomes 1, 6p, 9p, and 19q. A more recent comparative genomic hybridization study revealed recurrent enhancements on chromosome 20 and also found gain of chromosome 7 and loss of chromosome 10 in several cases of astrocytoma. Partial or complete gains of chromosome 20 were found in six other tumors, suggesting that chromosome 20, and in particular 20p11.2p12, may harbor relevant genes for glioma progression (Brunner et al., 2000). Bello et al. (1994) reported involvement of chromosome 1 in oligodendrogliomas and meningiomas; and Magnani et al. (1994) demonstrated involvement of chromosomes 1, 7, 10, and 19 in anaplastic gliomas and glioblastomas.

Loss of heterozygosity for loci on chromosome 17p (Fults et al., 1989) and 11p15 (Sonoda et al., 1995) have also been reported. Indeed, deletions of 17p have consistently been reported in as many as 50% of medulloblastomas, and the major breakpoint interval has been localized to 17p11.2, a chromosome instability that has been linked to hypermethylation in this region in medulloblastomas but not with supratentorial primitive neuroectodermal tumors (Fruhwald et al., 2001).

Comparative genomic hybridization has been recently utilized to review chromosomal imbalances in a series of 20 adult and 8 childhood ependymomas. All tumors exhibited multiple genomic imbalances with loss of genetic material observed in chromosomes 22q (71%), 17 (46%), 6 (39%), 19q (32%), and 1p (29%), with overlapping regions of deletion. These findings suggest greater genomic imbalance in ependymomas than earlier recognized and confirmed previous findings of frequent losses of 17 and 22q and loss of chromosome 16 as recurrent genetic aberrations found in these tumors (Zheng et al., 2000). Similarly, fluorescence in situ hybridization uncovered deletion of 22q12–q13 in two intracerebral ependymomas (Rousseau-Merck et al., 2000).

There are few data regarding chromosomal alterations in the peripheral blood lymphocytes of patients with brain tumor. Such information might shed light on the pre-malignant changes that herald tumor development. Bondy et al. (1996) demonstrated that, compared with controls, glioma cases have less efficient DNA repair, as measured by increased chromosome sensitivity to gamma radiation in stimulated peripheral blood lymphocytes, and that was shown to be an independent risk factor for glioma. Recently, we investigated whether glioma patients have an increased chromosomal instability that could account for their heightened susceptibility to cancer (El-Zein et al., 1999). With fluorescence in situ hybridization methods, background instability in these patients was measured at hyper-breakable regions in the genome. Findings indicate that the human heterochromatin regions are frequently involved in stable chromosome rearrangements (Larizza et al., 1988; Doneda et al., 1989). Smith and Grosovsky (1993) and Grosovsky et al. (1996) reported that breakage affecting the centromeric and pericentromeric heterochromatin regions of human chromosomes could lead to mutations and chromosomal rearrangements and increase genomic instability.

A study performed by El-Zein et al. (1999) demonstrated that individuals with a significantly higher level of background chromosomal instability have a 15-fold increased risk of developing gliomas. A significantly higher level of hyperdiploidy was also detected. Chromosome instability leading to aneuploidy has been observed in many cancer types (Lengauer et al., 1997). Although previous studies have demonstrated the presence of chromosomal instability in brain tumor tissues (Arnoldus et al., 1992; Mohapatra et al., 1995; Wernicke et al., 1997; Rosso et al., 1997), our study was the first to investigate the role of background chromosomal instability in the peripheral blood lymphocytes of patients with gliomas (El-Zein et al., 1999). Our results suggest that accumulated chromosomal damage in peripheral blood lymphocytes may be an important biomarker for identifying individuals at risk of developing gliomas.

CONCLUSION

In summary, the etiology of brain tumors remains largely unknown. Biologically intensive studies incorporating new molecular genetic techniques have the potential to increase our understanding of the etiology of gliomas. Use of more consistently applied histopathologic classification systems, and greater understanding and use of molecular and genetic markers to classify tumors, should help to delineate the natural history and pathogenesis of brain tumors. It is well known that primary brain tumors have many

causes; however, no single cause has yet been identified that can account for most cases. Many possibilities remain that will enable us to discover pertinent risk factors. Moreover, in the continuing search for explanations for this devastating disease, new concepts about neuro-oncogenesis will likely emerge, making the study of brain tumor epidemiology even more exciting.

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