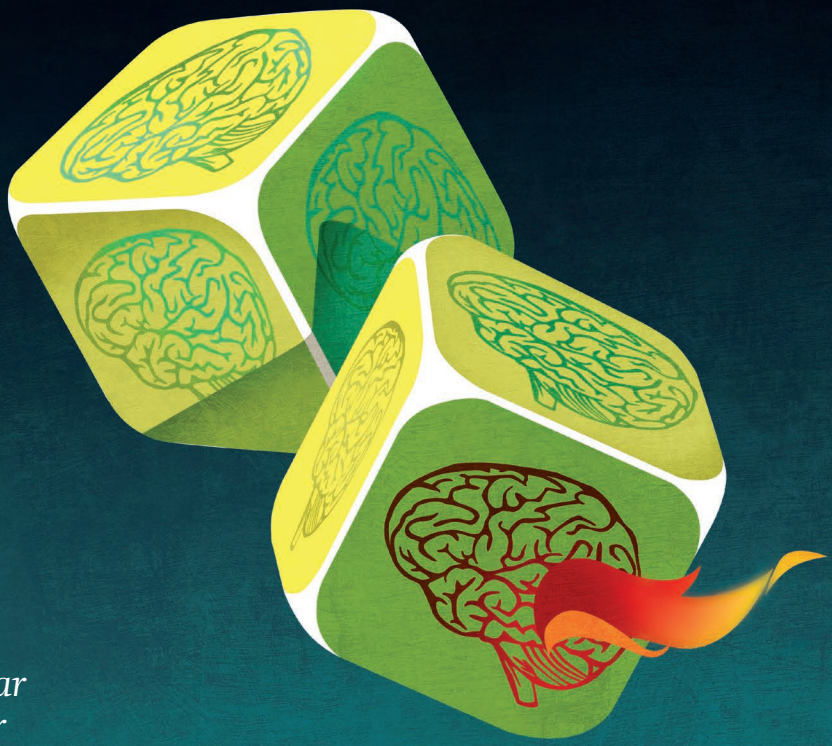
EPIDEMIOLOGY

Mysterious risk



Beyond the usual suspects, it's unclear which factors might increase or lower a person's chances of developing brain cancer. But researchers have turned up some intriguing clues.

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BY NEIL SAVAGE

To estimate your chances of developing brain cancer, take a look in the mirror. If you see an older white man, you are in the group that is at highest risk of this disease. If you have ever received radiotherapy for another head or neck condition, or have a close relation who has had brain cancer, your chances of developing such a tumour are greater still. But if you notice that your eyes are red from all the pollen you've inhaled, your risk of brain cancer might not be so high, after all.

A person's chances of developing brain cancer are low, regardless of the category into which they fall. In the United States, the lifetime chance of being diagnosed with a malignant tumour of the brain or spinal cord is less than 1%, according to the American Cancer Society.

Epidemiologists are unable to explain the causes of most brain cancers. They have identified a few genetic factors that place some people at higher risk (see page S54), as well as an external cause — ionizing radiation. And they have ruled out almost all environmental factors, including those implicated in many other cancers, although non-ionizing radiation from mobile phones has not been eliminated definitively. Along the way, they have discovered that some factors actually reduce the likelihood of developing brain cancer. Such factors offer tantalizing hints at fresh ways to screen for, or even to treat, the disease.

The International Agency for Research on Cancer (IARC) reported that there were 257,000 new cases of brain or nervous-system cancer worldwide in 2012 — an incidence of more than 3 cases per 100,000 people. Brain cancer is most common in white people, and its incidence is highest in northern Europe, at about 10 cases per 100,000, followed by the United States, Canada and Australia. Most of those cancers — roughly 80% — are gliomas, the most common and deadly type of which is glioblastoma multiforme (GBM). "We haven't gotten very far in terms of what we've learned about exposures or other risk factors, but we do know the demographics are different," says Melissa Bondy, an epidemiologist at Baylor College of Medicine in Houston, Texas.

RELATIVE RISK

There are two known risk factors for brain cancer. One is ionizing radiation, usually when delivered to the head or neck as treatment for various conditions that include other brain tumours. The other is a family history. People with certain inherited conditions that promote tumour formation, including neurofibromatosis and tuberous sclerosis, are at an increased risk. Such conditions cause about 5% of gliomas.

As well as those conditions, brain cancer itself can run in families. In 2008, Deborah Blumenthal, a neuro-oncologist at Tel-Aviv Sourasky Medical Center in Israel, analysed the medical and genealogical records of 1,401 people in Utah with brain cancer. She and Lisa Cannon-Albright at the University of Utah, Salt Lake City, found that having an immediate relative with GBM doubled a person's risk of developing the same disease[1]. People with close relatives who had a less aggressive form of astrocytoma had almost four times the risk of developing the same tumour. Blumenthal suggested that both the shared environment and shared genes might be to blame.

In 2015, the international study Gliogene, which Bondy leads, identified the first gene to be associated with familial brain cancer[2]. The gene, known as *POT1*, affects the length of telomeres — repetitive sequences of DNA at the ends of chromosomes that help to protect genes. Bondy is now investigating the part that *POT1* mutations play in brain cancer. But, she points out, only about 5% of brain tumours run in families.

Bondy has also looked at localized variations in the DNA sequence, known as single nucleotide polymorphisms (SNPs), that arise spontaneously in individuals. "Over 12,000 individuals, we've found 25 SNPs that seem to be predictive of risk of glioma," she

says. However, researchers are unable yet to say how much having one or more such SNPs increases a person's risk.

Strong links to environmental factors have been difficult for researchers to pin down. "We have studied a lot of different factors, over many decades, and we've ruled out a lot," says Jill Barnholtz-Sloan, a cancer epidemiologist at Case Western Reserve University in Cleveland, Ohio. Researchers have not been able to find a link with obesity, drinking alcohol, or exposure through food or in the workplace to certain metals, chemicals or pesticides. "We've studied all those and haven't found anything," Barnholtz-Sloan says. That might be because potential carcinogens must pass through several obstacles to reach the brain. "It's very well protected, compared to a lot of other organs."

THE PHONE QUESTION

A possible risk factor about which researchers remain undecided is radiofrequency electromagnetic fields generated by mobile phones. Some studies have hinted at an association with brain cancer, which was enough for the IARC to classify it as a possible carcinogen in humans, along with 301 other agents. (Notably, the IARC has judged 120 agents to be definitely carcinogenic and a further 82 as being probably carcinogenic.) Studies in male rats exposed discontinuously to high levels of mobile-phone radiation for nine hours a day over a period of up to two years found an increase in malignant schwannoma[3], a rare and usually non-lethal tumour type, in the animals' hearts. The relevance of this finding to glioma in people remains an open question.

Bondy is unconvinced. Since mobile-phone use became widespread in the late 1990s, organizations such as the Central Brain Tumor Registry of the United States have reported only a slight uptick in the incidence of brain cancer, which most researchers attribute to improvements in detection owing to advances in imaging technology. "The rates aren't increasing enough to say that electromagnetic exposure from cell phones increases risk of glioma," Bondy says.

There is also no known physical mechanism by which non-ionizing radiation, which imparts much less energy than its ionizing counterpart, can damage DNA. "Scientists have been looking for adverse health effects of radiofrequency fields since the 1950s, without finding much," says Kenneth Foster, an emeritus bioengineer at the University of Pennsylvania in Philadelphia, who has investigated the effects of such radiation. "If there is any increase in cancer risk from use of cell phones, it is quite small."

But the question is not settled, says Jonathan Samet, an epidemiologist at the Colorado School of Public Health in Aurora, who chaired the IARC working group that classified mobile-phone radiation as a possible carcinogen in 2011. Samet thinks it is notable that the recent studies in rats did find some biological effect, and says that the extensive use of mobile phones makes it worthwhile to continue such research.

NOTHING TO SNEEZE AT

In the search to provide support for risk factors, epidemiologists have turned up an intriguing finding. Certain conditions — including allergies, diabetes and chickenpox — seem to lower a person's risk of developing a brain tumour. Judith Schwartzbaum, an epidemiologist at the Ohio State University in Columbus, analysed blood samples deposited at a blood bank in Norway since 1972. She found that people who tested positive for the antibody immunoglobulin-E (IgE) were 25% less likely to go on to develop a glioma[4]. Women whose blood contained allergen-specific IgE had their risk of developing GBM cut in half. One hypothesis is that the immune system, already on the alert for the presence of allergens, is somehow able to stop brain cancer from gaining a foothold. Another possibility is that people with strong allergic reactions are better at eliminating carcinogens before they can cause damage to the brain.

Several other studies have found similar results. In 2016, Bondy, Barnholtz-Sloan and their colleagues looked at samples that were collected as part of the Glioma International Case-Control Study (GICC), the largest effort so far to study the disease, and found that having a history of respiratory allergies lowered a person's risk of developing glioma by about 30% (ref. 5). Asthma and eczema also significantly reduced the risk of glioma.

In an attempt to better understand the link between immunity and brain cancer, Schwartzbaum went back to the archived Norway blood samples and measured the levels of various immune-system proteins called cytokines in people with glioma, years before their diagnosis[6]. She expected to find that people who went on to develop glioma had lower levels of cytokine than did those who did not develop the cancer. In blood samples taken 15 years before diagnosis, much to her surprise, she observed little difference. But in samples taken five or fewer years before diagnosis, the mix of cytokines started to change. Whereas the correlation between these proteins in older samples was strong — for instance, if the level of one cytokine increased, that of another might decrease — there was a weaker correlation in samples from people who were only a few years away from diagnosis. "I think the immune system is responding to the tumour," Schwartzbaum says.

If she is correct — something that Schwartzbaum hopes to confirm by repeating the study on a different collection of blood samples — the finding might give doctors a way to detect glioma at an earlier stage. How useful that would be is unclear, however. Given the rarity of brain cancer and the lack of an easy follow-up diagnostic test, broader screening programmes might not be practical. And even if they were, researchers would still need to show that early detection leads to improved outcomes.

There might be more of a pay-off from teasing out other intriguing associations. In 2017, Schwartzbaum confirmed the presence of an inverse relationship between glioma and blood-glucose levels in people with diabetes[7]. "A lot of people believe that it's due to medication," she says. She plans to look at a large data set to determine whether metformin, a drug that is commonly prescribed to treat diabetes and that also seems to interrupt certain processes involved in tumour growth, is associated with a reduced risk of brain cancer.

Another finding to emerge from the GICC was that catching chickenpox lowers a person's risk of glioma by 21% (ref. 8). When combined with the allergy findings, this "suggests the immune system is suppressing the tumour", Schwartzbaum says. Working out the mechanism behind that suppression could eventually lead researchers to fresh targets for treatments. It is unclear whether the varicella-zoster-based vaccine used to prevent chickenpox has the same effect on the risk of developing glioma, but if it did, the vaccination might be recommended to help prevent brain cancer, akin to the way in which the human papilloma virus vaccine is used to lower the risk of cervical cancer.

As doctors and researchers develop a better appreciation of the diversity of brain cancer, it is becoming more challenging for epidemiologists to tease out relevant risks. Categorizing such cancers into subtypes that might have different causes, and then cross-checking for potential risks when several factors might be interacting, could require thousands or even tens of thousands of cases. "It's likely an interplay between genetics and things in your environment and lifestyle, and the mathematics of that is complicated," says Barnholtz-Sloan.

Schwartzbaum hopes that molecular biology could yet reveal some unknown risk factors. Large studies, including the Million Veterans Project, conducted by the US Department of Veterans Affairs, although not geared specifically to studying brain cancer, could uncover useful evidence. But only, Schwartzbaum says, if there are indeed more risk factors to be found. "Maybe it's just bad luck — you get a mutation and that's it," she says. "But I'd like to make sure that's true, because if we can find something, maybe we can prevent it." ■

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