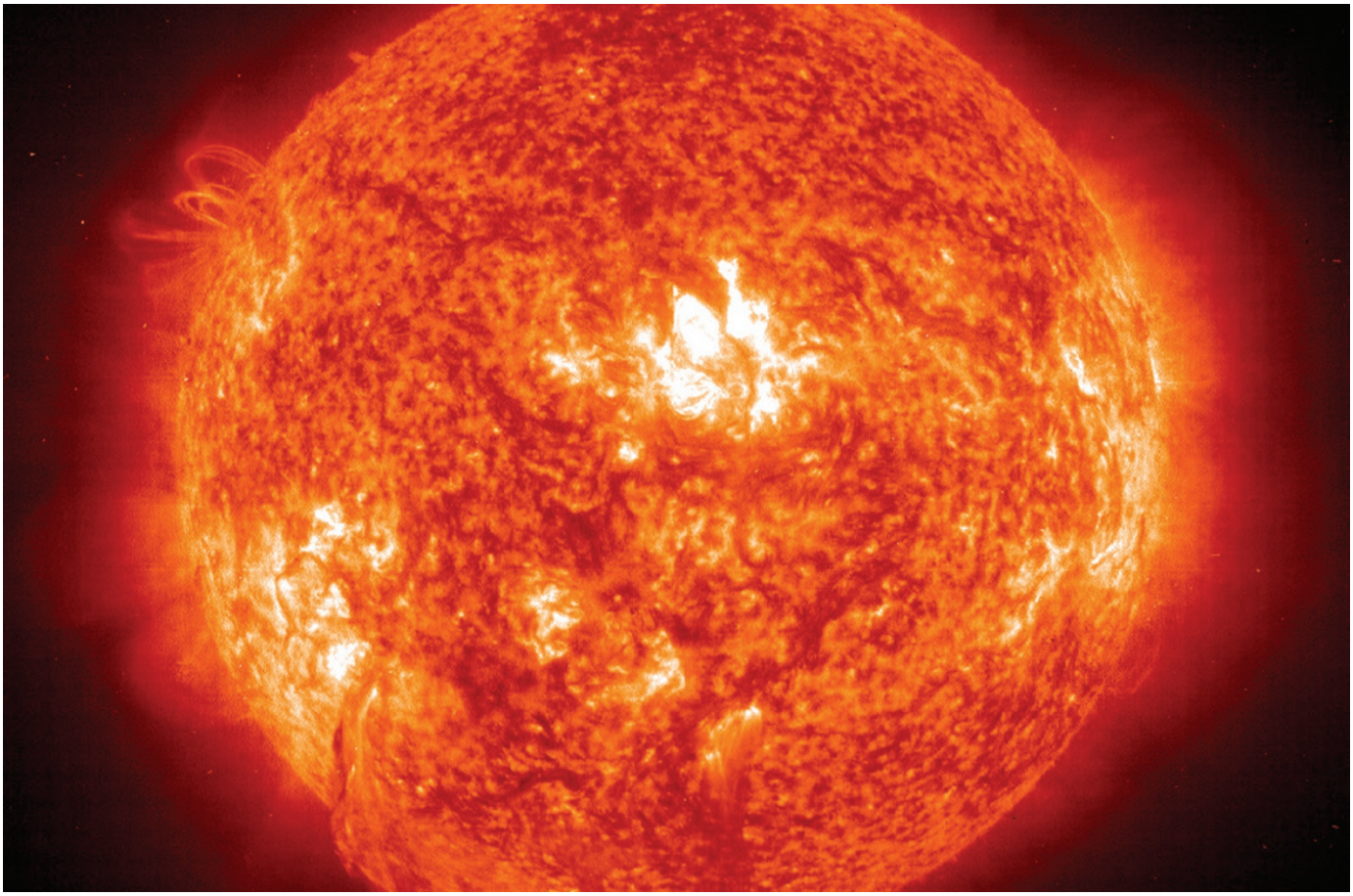

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The timing and pattern of exposure to the sun can alter the chance of someone developing melanoma.

RISK FACTORS

Riddle of the rays

Spending time in the sun is a major risk factor for melanoma, but the relationship is not as straightforward as it seems.

BY CASSANDRA WILLYARD

People all around the world have been bombarded with the message that the single biggest risk factor for skin cancer is spending time in the sun, and that limiting their exposure is the best way to stay safe. In Australia, a cartoon seagull advised people to slip on a shirt, slop on some sunscreen, and slap on a hat. In Dubai, one advertising agency distributed coffin-shaped beach towels printed with the words: "Over-exposure to the sun causes skin cancer killing 20 people every day." And posters in Canada proclaim: "No tan is worth dying for!" But although the link between sun exposure and melanoma is clear, it is far from straightforward.

Consider, for example, Merideth Cooper, a 24-year-old graduate student who discovered a suspicious mole on her back while shopping for bras. A week later she went to the doctor to have the mole removed, along with another suspicious mark on her thigh. Both turned out to be melanomas. But the diagnosis did not seem to make sense. Cooper had been to the tanning salon a few times but wasn't a regular user. And she had been sunbathing during the spring break, but she was not one of those girls who spent her summers lying in the sun. "I know people who are out in the sun way more," she says.

The damage that triggers melanoma often starts with the absorption of ultraviolet radiation, so it makes sense that more sun would confer more risk. But that is not always true. The timing and pattern of exposure are also crucial. Furthermore, some individuals are more susceptible than others. "When you put all those factors into the mix, it can make a complicated story," says David Whiteman, a melanoma researcher at QIMR Berghofer Medical Research Institute in Herston, Australia. While Whiteman and other epidemiologists try to make sense of this complexity, some researchers are exploring the role of other environmental risk factors.

SPORADIC EXPOSURE

Melanoma begins in melanocytes, the cells that give skin its colour. These cells contain a pigment called melanin, which absorbs damaging ultraviolet rays from the sun. Exposure to the sun drives most forms of the disease, but the connection is complicated. "Melanoma is not one disease, it's a collection of diseases," says Martin Weinstock, a dermatologist at Brown University in Providence, Rhode Island, and they have different risk factors. For example, the rare melanomas that arise on the palms of the hands or the soles of the feet, on mucous

membranes, or under fingernails and toenails, don't seem to be linked to ultraviolet exposure (see page S121).

But even for the most common forms of the disease for which sun exposure is a known risk factor, the data can be confusing. "You might expect that if you work in the sun all day, if you're a gardener or something, that you might have particularly high rates of melanoma," says Anne Cust, an epidemiologist at the University of Sydney in Australia. "But that doesn't seem to be the case." Indeed, some studies have found that outdoor workers actually have a lower risk of developing melanoma than those who work indoors[1,2].

Instead, the greatest risk seems to come from intermittent sun exposure and sunburn, and the use of sunbeds. One Canadian study, for example, found a strong link between activities associated with intermittent exposure, such as beach vacations, and an increased risk of melanoma[3].

Researchers are still trying to tease out why that might be. One idea is that skin exposed continuously to sunlight adapts and becomes better at repairing the DNA damage caused by ultraviolet radiation. Another idea is that the increased production of melanin might form a protective shield against the harmful rays.

"You might expect that if you work in the sun all day you might have high rates of melanoma. But that doesn't seem to be the case."

But a more controversial hypothesis involves vitamin D. Sunlight helps the body to synthesize its own vitamin D, and some researchers think that people who spend a lot of time outdoors might be protected from developing melanoma by having higher levels of the vitamin. But the evidence is limited and the causality is ambiguous. "We still haven't decided whether vitamin D is the result of good health, or whether it leads to good health," says Marianne Berwick, a cancer epidemiologist at the University of New Mexico in Albuquerque.

TWO ROADS DIVERGE

Furthermore, not every study has found a strong link between intermittent sun and melanoma. Whiteman thinks this is because intermittent exposure is only part of the story. Over the past decade, he has been analysing where and when melanomas occur, and he has found additional nuances. For example, chronic exposure does seem to be a risk factor, but only for certain people. Outdoor workers tend to get their melanomas on exposed areas of skin — the face, ears, neck and scalp — when they are in their 70s and 80s. People who develop the disease earlier in life tend to have had more episodes of acute sun exposure early in life, he says. In this group, melanoma tends to occur in parts of the body that are only occasionally exposed to the sun, such as the back, abdomen, upper legs and arms.

Whiteman argues that these differences are at least partly due to differences in people's propensity to develop moles. It makes sense that a greater tendency to develop moles may indicate the presence of melanocytes that readily proliferate. Indeed, individuals who have more moles have a higher risk of melanoma. In these people, Whiteman says, short bursts of intense sunlight early in life might be enough to kickstart the molecular events that lead to the cancer. Melanocytes are still maturing in young people, and those on the trunk seem to mature more slowly. In people who do not tend to develop moles, however, the process might require more prolonged sun exposure. Whiteman calls this hypothesis the 'divergent pathways' model.

In 2003, Whiteman attempted to test this model. He compared people who developed malignant melanomas on their trunks with people who had them on their heads and necks. Almost everyone in the study had at least one mole, but those with melanomas of the head and neck tended to have fewer moles than those who developed melanomas on their trunk. They also reported greater occupational sun exposure[4]. A handful of other studies have reported similar results (see ref. 5, for example).

Whiteman is still refining his theory. "Initially, our model was that there are two pathways," he says. But molecular investigations suggest that there are more than that, and that different patterns of sun exposure damage different genes. "As we combine our knowledge of molecular science with epidemiology, we can start to untangle these pathways a bit more clearly," he says.

BEYOND THE SUN

We know that sunburn — a marker of intermittent exposure — seems to roughly double an individual's risk of developing melanoma. But we don't know whether other environmental factors play a role too. "You would think that if the sun were the only cause it would be much stronger, as in cigarette smoking and lung cancer," Berwick says. (Smokers are 15–30 times more likely to develop lung cancer than those who do not.)

Studies in the 1980s and 1990s examined the relationship between people's workplace and their risk of developing different types of cancer. Some studies found a potential link between melanoma and organic chlorine compounds, a class of chemicals that includes PCB, an industrial chemical that was banned decades ago.

Richard Gallagher, an epidemiologist who studies cancer risk at the BC Cancer Agency in Vancouver, Canada, decided to revisit the link using existing data and blood samples. He and his colleagues found that those with the highest levels of PCBs in their blood had a sixfold greater risk of melanoma than those with the lowest concentrations[6]. Gallagher is working on a larger study to see if the association holds, but the link to PCBs seems plausible. "They can produce reactive oxygen species, and perhaps that renders people more susceptible to other factors," he says. Although PCBs are no longer sold, they are still found in the environment, with fish in particular containing high levels of the pollutant.

Frank Meyskens, an oncologist at the University of California, Irvine, thinks there may be another culprit: heavy metals, especially chromium. He became suspicious when he read that melanoma is unusually common in patients who have metal-on-metal hip replacements composed of alloys that contain cobalt and chromium. The US Food and Drug Administration warns that when the ball and cup of these hips slide against each other, they can release metal particles, some of which end up in the bloodstream. When Meyskens and his colleagues incubated melanocytes in the presence of a variety of metals, they found that cells exposed to chromium changed their shape and developed chromosomal abnormalities[7], supporting the idea that these metals can cause skin cancer.

Certain medications have also been implicated. This summer, a team of researchers from Harvard University in Boston, Massachusetts, found a link between malignant melanoma and sildenafil citrate (Viagra). The study followed nearly 26,000 men over 10 years. Men who had taken the drug were twice as likely to develop melanoma as those who did not. The drug inhibits a molecule called PDE5A, and the team speculates that this might promote the invasion of the primary tumour[8].

Other environmental factors might provoke the disease too. Cooper, who is now free of cancer, will never know the exact cascade of events that sparked her melanoma. But now that she has had the disease, she has an increased risk of recurrence, so she takes precautions. When she is out in the sun, she always wears hats and uses sunscreen. She keeps an inventory of her moles and is constantly looking out for changes. "I notice everything now," she says. "You have to almost be that cautious because you have to catch them early." ■

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