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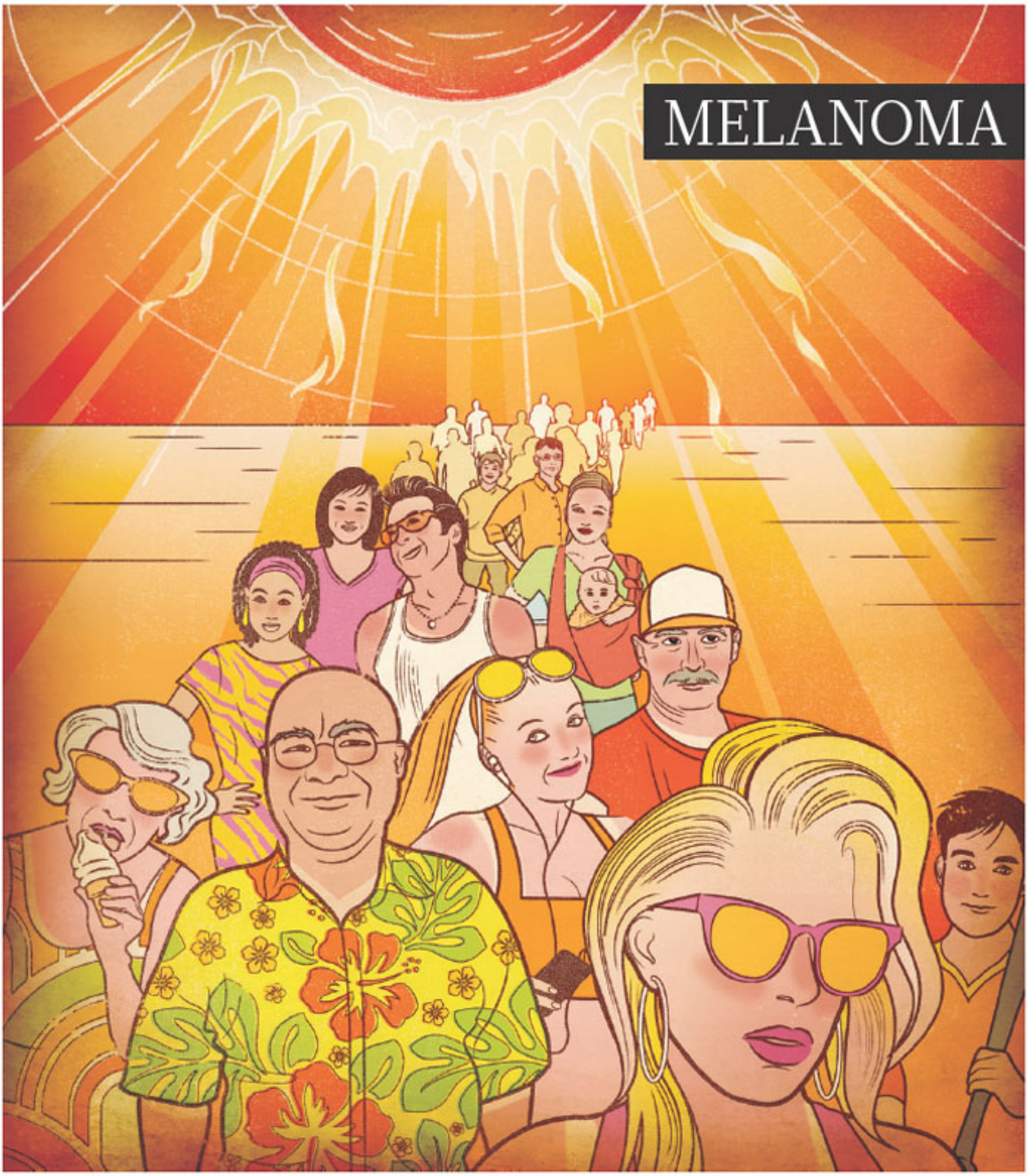

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Shining a light on skin cancer

nature OUTLOOK

MELANOMA

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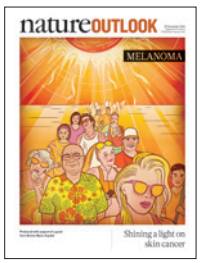

Cover art: Susan Burghart

Melanoma is the deadliest form of skin cancer and strikes tens of thousands of people around the world each year. The number of cases is rising faster than any other type of solid cancer (see page S110).

It is usually caused by too much exposure to the Sun's ultraviolet radiation. But the link between sunshine and melanoma is not as straightforward as it seems. The pattern of exposure can be just as important as the total amount of ultraviolet radiation that reaches the skin (S112).

Because the cause of melanoma is so well known, it seems strange that the incidence keeps rising. But although we have the tools to prevent the disease, we do not always use them (S117 and S126), and not enough people take action to reduce their risk. Australia, which has the highest rate of melanoma, has been slowly getting the disease under control and may have some lessons to teach the rest of the world (S114).

For those hoping to skip the demands of a sun-safe routine and simply take a sunscreen pill instead, the news is not so good. There is little evidence that any drug will be able to offer full sun protection (S124).

For those who do develop melanoma, however, the chances of recovery are rising. Targeted treatments and therapies that use the body's own immune system have been developed in the past few years (S118).

Although melanoma is primarily an affliction of the fair-skinned, it can also strike those with a darker complexion. The disease in black populations seems to have a different biology to that in lighter-skinned people, and is also particularly deadly (S121).

We are pleased to acknowledge that this Outlook was produced with support of a grant from Bristol-Myers Squibb. As always, *Nature* retains sole responsibility for all editorial content.

Brian Owens
Contributing Editor

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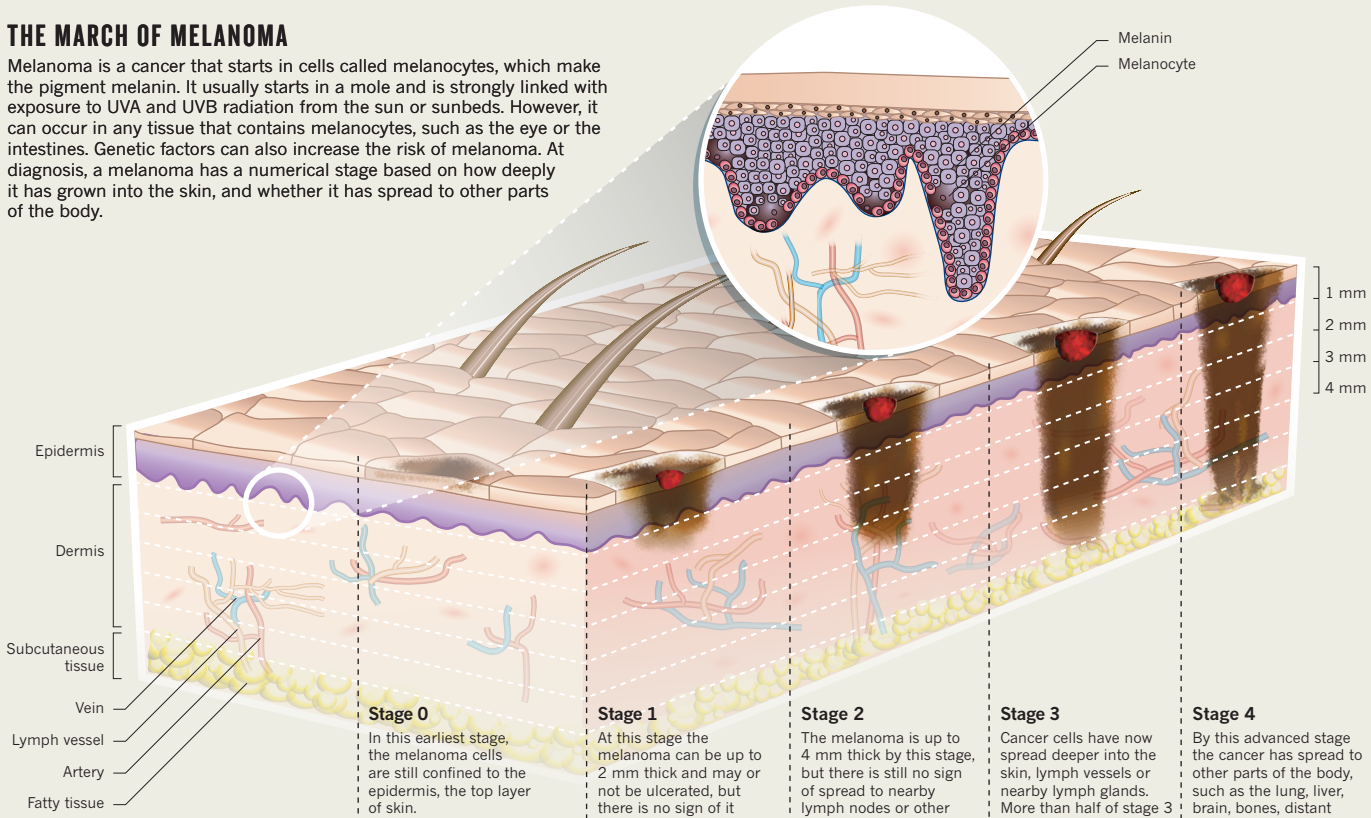
COLLECTION

THE CANCER THAT RISES WITH THE SUN

Melanoma is an aggressive cancer that normally starts in the skin. It can strike anyone but is most common in people with pale skin, and it is getting more common. By ***David Holmes****.*

THE MARCH OF MELANOMA

Melanoma is a cancer that starts in cells called melanocytes, which make the pigment melanin. It usually starts in a mole and is strongly linked with exposure to UVA and UVB radiation from the sun or sunbeds. However, it can occur in any tissue that contains melanocytes, such as the eye or the intestines. Genetic factors can also increase the risk of melanoma. At diagnosis, a melanoma has a numerical stage based on how deeply it has grown into the skin, and whether it has spread to other parts of the body.



Stage 0
In this earliest stage, the melanoma cells are still confined to the epidermis, the top layer of skin.

Stage 1
At this stage the melanoma can be up to 2 mm thick and may or not be ulcerated, but there is no sign of it spreading to lymph nodes or other parts of the body. It can be easily removed by surgery.

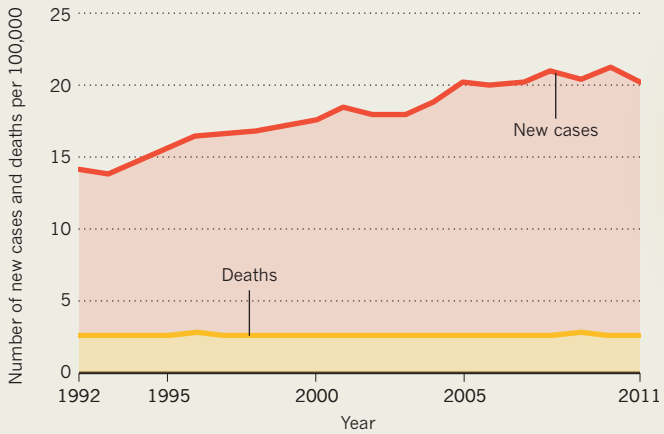
Stage 2
The melanoma is up to 4 mm thick by this stage, but there is still no sign of spread to nearby lymph nodes or other sites. Most stage 2 melanomas can still be treated with surgery.

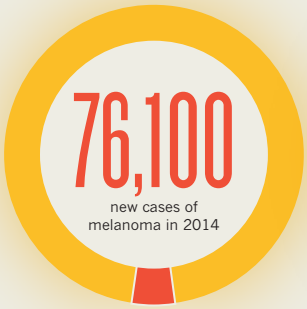
Stage 3
Cancer cells have now spread deeper into the skin, lymph vessels or nearby lymph glands. More than half of stage 3 melanomas come back after surgery.

Stage 4
By this advanced stage the cancer has spread to other parts of the body, such as the lung, liver, brain, bones, distant lymph nodes, or other areas of the skin. Treatment depends on which areas are affected.

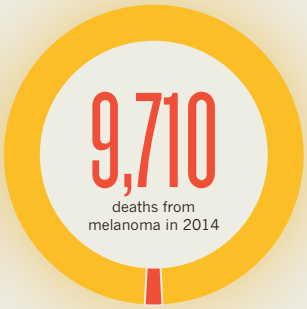
INCREASING BURDEN

The incidence of melanoma is increasing faster than that of any other solid tumour, although the mortality rate has remained largely flat. Figures shown are for the United States, where melanoma is now the fifth most common form of cancer.





4.6%
of new cancer cases

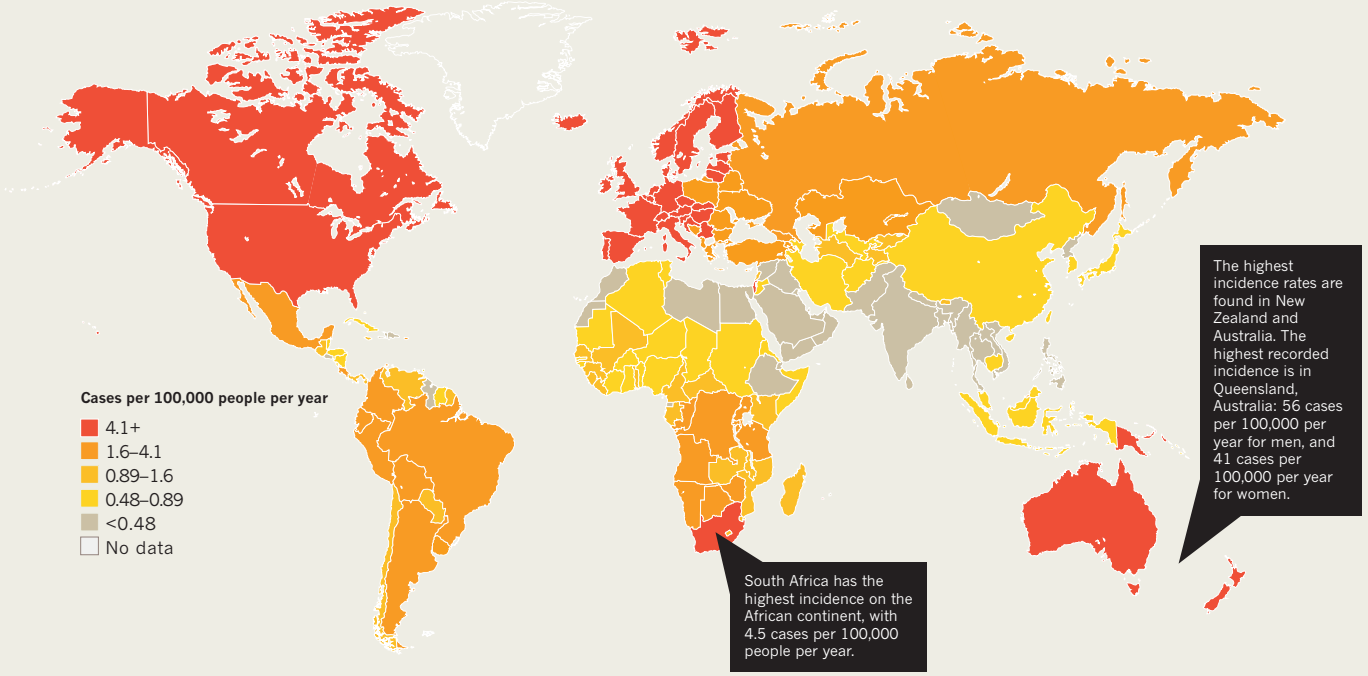


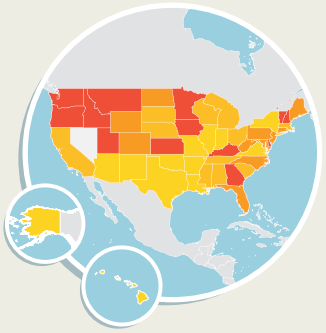
1.7%
of deaths from cancer

SOURCES: Cancer Research UK/Surveillance, Epidemiology, and End Results Forum

GLOBAL INCIDENCE

Melanoma is the 19th most common cancer worldwide, with around 232,000 new cases diagnosed in 2012, accounting for 2% all cancers. The highest rates of melanoma occur in countries where the inhabitants are predominantly light skinned. Northern Europe and North America have the highest incidence rates in the Northern Hemisphere, and Australia and New Zealand have the highest incidence in the south. The burden of melanoma in South America and Asia is relatively low.



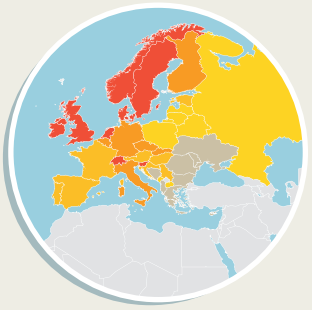


United States incidence map

The highest rates of melanoma in the United States occur in the northwest and southeast states, reflecting the higher proportion of the population who are of non-Hispanic white ethnicity in those states.

Cases per 100,000 people per year

- 22.9–34.1
- 20.5–22.8
- 18.5–20.4
- 9.0–18.4
- No data



Europe incidence map

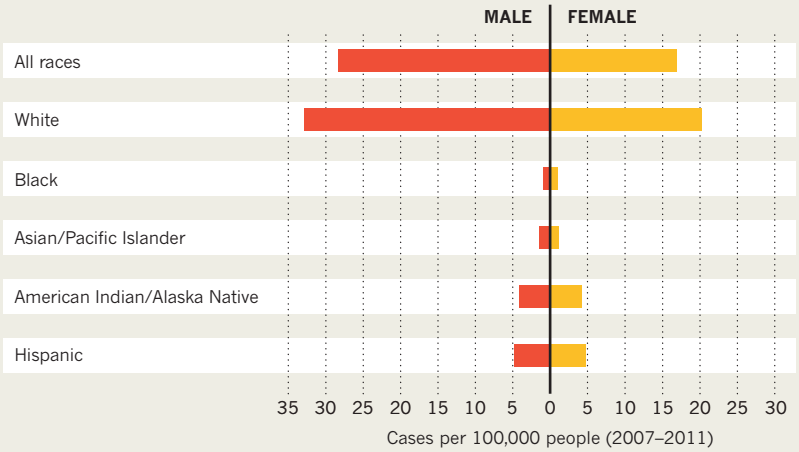
Switzerland has the highest incidence of melanoma in Europe, with 25.8 cases per 100,000 people per year. Southern European populations have the lowest burden of melanoma. The incidence is highest in Northern Europe, particularly in nordic countries.

Cases per 100,000 people per year

- 16.9+
- 13.1–16.8
- 7.7–13
- 5.3–7.6
- <5.3

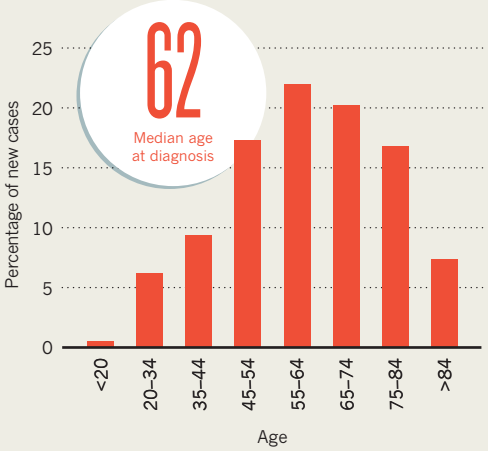
BEYOND THE PALE

Anyone can get melanoma but it usually afflicts people with light skin, and it is more common in men than in women. In the United States, it is more common among non-Hispanic whites than people of other races and ethnicities.

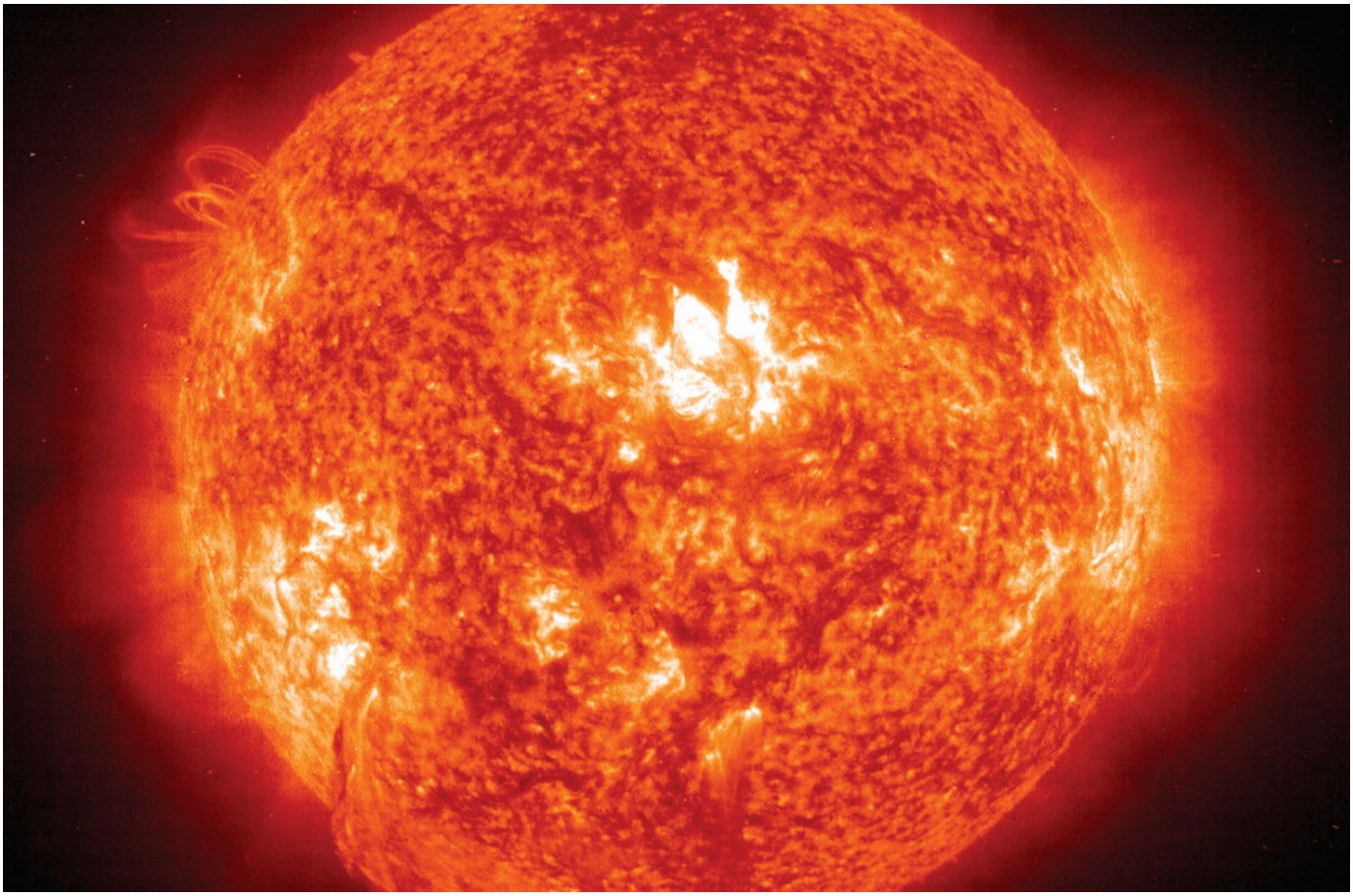


TIME IN THE SUN

In the United States, melanoma of the skin occurs most often in people aged between 55 and 64.



SOURCES: WHO International Agency for Research on Cancer/Globocan/Eucan/US Centers for Disease Control and Prevention



SOHO/ESA/NASA

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." ■

Cassandra Willyard *is a freelance writer based in Madison, Wisconsin.*

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NIGEL HICKS/GETTY

The rewards of sunbathing can be immediate but the melanoma risk may seem distant and intangible.

PREVENTION

Lessons from a sunburnt country

Countries that can't persuade people to stay safe in the sun could learn from Australia, melanoma capital of the world.

BY ZOË CORBYN

Before she leaves home in San Francisco, California, Jennifer Schaefer dons long sleeves and a big hat she calls her "personal umbrella". With her fair skin, red hair, memories of bad childhood sunburn, and a family history of skin cancer, Schaefer is painfully aware of the dangers of exposure to ultraviolet radiation, which accounts for the vast majority of skin cancers.

So she finds it mind-boggling how few people bother with sun safety, with most preferring sun worship to sun protection. "In our culture, it's almost funny to be too sun protected," she says, highlighting the way her friends tease her when she dons her bathing suit — a protective 'rash guard' top and knee-length board shorts. "We're slowly starting to become aware of the long-term effects of the sun, but it's like global warming — people are not going to make serious changes until they feel a direct impact."

That impact has helped push Australians, who are famous for sun loving, into changing their behaviour. With its high solar ultraviolet levels and predominantly fair-skinned population, Australia has the highest rate of skin cancer in the world. But after decades of increase, the melanoma rate began to plateau in the mid 1990s[1]. The incidence of melanoma among young people is now falling[1,2], as national surveys show that most Australians — more than 70% of adults and 55% of adolescents — no longer prefer a tan[3].

SLIP! SLOP! SLAP!

One reason for the change is that Australia essentially hit saturation point, says Adèle Green, a cancer epidemiologist at the QIMR Berghofer Medical Research Institute in Brisbane. Melanoma was so common that most people knew someone who had suffered from it, so the need to act was obvious. There has also been an ongoing skin-cancer awareness campaign to educate the public[4,5] that started in the early 1980s with the well-known 'Slip! Slop! Slap!' television commercial, in which an animated seagull told Australians how to stay safe in the sun. The SunSmart programme today combines mass media campaigns and intensive work with schools, workplaces, local government, health professionals, parents and sports groups. Operating under the control of charities called cancer councils, with funding from state governments, the SunSmart programme has made Australia a world leader in preventing skin cancer.

When Green was growing up, annual sunburn for children was "just a fact of life", she says. As a teenager, she and her friends cooked themselves "like bacon and eggs" in suntan oil. Melanoma rates are still increasing among older people[1] because damage done early in life can trigger malignancy decades later. But Green believes there has been a national change in mindset. "Generations born since 'Slip! Slop! Slap!' have known nothing but a culture imbued with sun protection messages," she says.

Many other countries struggling to get their populations to make sun protection part of daily life would love a little of Australia's magic. In July 2014, the US surgeon general issued a 'call to action' (go.nature.com/zy27zl) asking all sectors of society to come together to reduce exposure to ultraviolet radiation. "One of the reasons we put this report out is to do what Australia did years ago," says Boris Lushniak, acting US surgeon general. The report details increasing rates of skin cancer and says most people are not doing enough to protect themselves from the sun. One in three adults has had sunburn in the past year, it says. It also points to the high use of sunbeds by young white women, with nearly one in three

QUEENSLAND DEPARTMENT OF HEALTH

engaging in the practice each year (see 'Banning indoor tanning').

"We have increased knowledge but there is not a lot of evidence for changing behaviour," says Joel Hillhouse, a psychologist who directs the Skin Cancer Prevention Laboratory at East Tennessee State University in Johnson City. So why aren't people in the United States and elsewhere heeding the messages? What lessons can be learned from Australia?

One powerful obstacle to people protecting their skin properly is our culture's view that a tan is attractive and healthy. "The social perception that tans are beautiful is a barrier we still as a society haven't overcome," says Eleni Linos, a dermatologist who studies skin-cancer prevention at the University of California, San Francisco. Perpetuating this notion, says Hillhouse, is a multibillion-dollar tanning industry.

Then there is the nuisance factor: protecting skin requires steps such as remembering a hat or applying sunscreen that can seem more trouble than they're worth[6]. The risk–reward balance works against sun protection in many people's minds, says Carolyn Heckman, a psychologist specializing in skin-cancer prevention at the Fox Chase Cancer Center in Philadelphia, Pennsylvania. The risk of skin cancer can seem minor, distant and intangible. By contrast, tanning can provide instant gratification.

But there is nothing immutable about people's affinity for the sun. Indeed, until the early 1900s, pallor was popular in Europe and North America because it indicated an upper-class lifestyle and an occupation that did not entail outdoor labour (this idea still prevails in many Asian countries). Then in the 1920s doctors began prescribing sunbathing as medication for ailments such as tuberculosis. Many people credit French style icon Coco Chanel with making the tan chic by bronzing herself on a yacht in the Mediterranean. By the 1960s the bikini had arrived, and tanning beds further increased the population's exposure to ultraviolet radiation.

"We have increased knowledge but there's not a lot of evidence for changing behaviour."

But our love of the sun is more than just cultural. Our biology makes it hard to stay away too. Frequent sunbathers and indoor tanners can exhibit symptoms of addiction. Mice exposed to a daily dose of ultraviolet radiation develop higher levels of the feelgood hormone β-endorphin within a week, and exhibit classic symptoms of withdrawal when the endorphin rush is blocked[7]. This effect may explain why it feels good to go out on a sunny day, says David Fisher, director of melanoma research at Harvard University in Cambridge, Massachusetts, who led the mouse study. He believes it could be a relic of our evolution, dating back to when being outside in the sun could have conferred health benefits and even saved lives by triggering the skin to synthesize the vitamin D required for strong bones.

Australian primary schools typically provide plenty of shade and encourage children to wear sun hats.

"Per exposure, the power of the euphoric effect is pretty small," Fisher says. "But if people have just a modestly increased propensity to seek ultraviolet radiation, over a population of millions you have an increase in skin cancer." Recognizing the addictive effect, he believes, could aid public-health efforts. For example, he argues that regulatory agencies should take a tougher stance with young people on sunbeds because of the possibility of dependence. And public-health messages could be enhanced by explaining to people that our physiology means we have less control than we think. "It might allow people to step back and look more objectively at their behaviour," he says.

MIXED MESSAGES

Inconsistent public-health messages may also be hampering behavioural change. In 2012, DeAnn Lazovich, a cancer epidemiologist at the University of Minnesota in Minneapolis, compared the recommendations to prevent skin cancer from four US health bodies[8]. They sometimes had different messages and ranked the order of protective actions differently. "Anyone trying to figure out what they ought to do might be a little bit confused," she says.

Linos is worried by a general overemphasis on sunscreen, the most common protective measure people take. Her research shows that sunscreen users get sunburn more frequently than those who seek shade or wear protective clothing[9]. Although people may be more likely to apply sunscreen before prolonged exposure to the sun, she acknowledges, they often fail to apply it thickly enough to be effective. It can also lull users into a false sense of security. "People feel they can stay out longer," she explains.

Contradictory information about vitamin D has added to the confusion, says Martin Weinstock, a dermatologist and community-health researcher at Brown University in Providence, Rhode Island. There have been suggestions that vitamin D can help prevent everything from cancer to diabetes (although a 2010 Institute of Medicine report found insufficient evidence for any beneficial effect beyond bone health), and the tanning industry has seized on this, says Weinstock. So the public hears warnings about the need for sun protection juxtaposed with messages about the benefits of vitamin D. "It doesn't take much contradictory messaging to really screw up the whole enterprise," Weinstock says.

Different countries resolve this conflict in different ways. The United States has encouraged people to protect themselves from ultraviolet radiation and to get any additional vitamin D they need from supplements. But Australia advises people that they may need to seek sun exposure to ensure adequate vitamin D levels, which they can do safely by going

outdoors without sun protection at times of day when ultraviolet levels are low. This 'do no harm' approach is balanced and realistic, says Craig Sinclair, who heads prevention at Cancer Council Victoria in Australia. But Weinstock disagrees, arguing that there is no guaranteed safe level of ultraviolet exposure. "A little bit of sun is not going to do you a lot of harm, but it will do you a little bit of harm," he says.

What's more, public-health messages haven't always been well designed for the demographic groups they are intended to target. Hillhouse has studied what motivates young women who use sunbeds to change their behaviour, and it has little to do with their health[10]. "A young person's view of skin cancer is that it is just so far off," he says. It's better to focus messages on something they care deeply about: their appearance. For young women, Hillhouse advocates stressing the link between ultraviolet exposure and wrinkles and, importantly, suggesting safe alternatives to achieve a socially desirable appearance, such as exercise. "Public health tends to take an almost religious view — you just tell people what is going to make them healthier and they will do it," he says. But that approach is flawed, Hillhouse explains. "Psychology says we need to work with the person in ways that matter to them."

BANNING INDOOR TANNING

The campaign against sunbeds

It is hard to overstate Clare Oliver's role in Australia's campaign against sunbeds. She was a 26-year-old journalist who died of melanoma in late 2007, but she devoted the last month of her life to publicizing the dangers of indoor tanning, which she blamed for her melanoma. The media frenzy that followed her appearance on television led the state of Victoria to become the first in Australia to announce it would ban people younger than 18 from using commercial tanning beds. Other states soon followed, but what Oliver started didn't stop there — at the end of 2014, all Australian states will ban commercial indoor tanning completely. Australia will be the second country after Brazil, which took action in 2009, to have imposed such a ban. The World Health Organization classified sunbeds as carcinogenic in 2009.

Many European countries have also legislated to ban access to sunbeds for minors, including the United Kingdom (Scotland in 2009, England and Wales in 2011, and Northern Ireland in 2012). The ban couldn't come soon enough. It is well established that melanoma incidence is lower in the north of England than in the sunnier south, but the high prevalence of indoor tanning among young women in the north of England is thought to be one reason why they buck the trend[11].

Eleven US states, led by California in 2011, have prohibited indoor tanning for those under the age of 18 (others have weaker restrictions and 10 states have none at all). In May 2014, the US Food and Drug Administration reclassified tanning beds from low risk (class I) to moderate risk (class II) , and it now requires manufacturers to include a warning advising against their use for people younger than 18. "Society makes the decisions," says Boris Lushniak, the acting US surgeon general. "But this is needless exposure to ultraviolet radiation, a known carcinogen." **Z.C.**

AUTOMATIC FOR THE PEOPLE

One lesson Australia can teach other countries, says Sinclair, is that prevention campaigns require sustained resources. "Every time we take our foot off the pedal and reduce our investment, we get a regression in behaviour," he says.

Indeed, funding for prevention campaigns in the United States has only ever been sporadic — there has never been a serious national campaign. "The resources we have put into stopping smoking, drunk driving or AIDS have never been put into skin cancer," says Hillhouse. In the United Kingdom, where rising skin-cancer rates are thought to be driven by the popularity of cheap overseas travel and indoor tanning[1,11], the charity Cancer Research UK has run a prevention campaign for the past decade. It is based on Australia's SunSmart brand but the investment has only been "very small" in comparison, says Sinclair. Yet prevention provides value for money by reducing expensive treatment costs: every Aus$1 spent on SunSmart in Australia delivers a net saving of $2.30 (ref. 12).

Another important lesson — also apparent from anti-smoking campaigns — is that an educational component alone is not enough. Mass media campaigns targeted at changing individuals' behaviour have to be backed by policies and legislation. "Just personal choice is not going to do it," says Green. Australian primary schools, for example, have adopted 'no hat, play in the shade' policies, and also have commitments to provide sufficient shade in school grounds. Sunscreen is available in classrooms, and sun protection is taught to children of all ages. By contrast, many US primary schools ban hats on the school grounds (partly to discourage cliques) and only allow sunscreen to be dispensed by a school nurse. "We would like those students to be allowed to use proper sun protection," says Lushniak.

Australia has succeeded, says Linos, because it has coupled its educational campaign with efforts to make it easy to use sun protection. "If you make it automatically part of daily life it is much easier," she says. It takes less effort to stay in the shade where there is plenty available, to pay attention to the ultraviolet index when it is part of the weather forecast, and to persuade children to wear hats when they are used to wearing one at school.

Meanwhile there is some cause for optimism outside Australia. Attitudes have started to change. Hillhouse says he has unpublished US data showing that a mild, rather than dark or moderate, tan is now preferred. In his study, participants sought "just enough tan to take away the pale look". And analysis of American women's fashion magazines over several decades shows that models are not as tanned as they used to be[13].

A 2013 study shows that, in addition to Australia, a handful of countries — notably New Zealand, Canada, Israel, Norway, the Czech Republic (for women) and the United States (for white men) — have melanoma rates that are declining or stabilizing among young people[1]. "Very slowly we seem to be turning the tide," says Green.

Researchers say the US surgeon general's call to action will need to be backed by funding to have the greatest effect, but they hail it as a step in the right direction. Sun safety "has been elevated to a public-health priority now", says Lazovich. "It gives groups something to get behind," adds Weinstock.

Back in San Francisco, Jennifer Schaefer is doing her best to educate the next generation. Her eldest daughter automatically puts on a hat to go outside. "Habits really start in childhood — it is like brushing your teeth," she says. ■

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PERSPECTIVE


Catch melanoma early

The United States and other nations should follow Germany in routine skin screening, say **Susan M. Swetter** and **Alan C. Geller**.

Melanomas can be treated most effectively if they are caught early when they are thinner. The best way to make sure this happens is to have a doctor or other health-care provider perform skin examinations, rather than to rely solely on the patient.

However, in 2009, a lack of clinical-trial data on the effect of screening on melanoma mortality left the US Preventive Services Task Force (USPSTF) unable to recommend routine skin-cancer screening of the general population by primary-care doctors. The USPSTF pointed out that the harms of such screening — such as physical and psychological effects related to misdiagnosis, overtreatment and unnecessary biopsies — had not been adequately addressed.

Since then, however, evidence for improved outcomes following skin screening has mounted. A population-based study of the residents of Queensland, Australia, with first primary invasive melanoma (which invades the deeper layers of the skin) showed a 40% lower risk of being diagnosed with thick (≥3 mm) melanoma if a skin exam was performed in the three years before diagnosis[1], resulting in a predicted 26% fewer melanoma deaths over five years.

An employee education and screening programme at the Lawrence Livermore National Laboratory from 1984 to 1996 was associated with a nearly 70% reduction in thick melanoma diagnosis and significantly fewer melanoma deaths in the workforce than expected according to California mortality data[2]. A subsequent multicentre observational study of 566 US adults with invasive melanoma found that patients who underwent a full-body skin examination by a physician in the year before diagnosis were twice as likely to have a thinner (≤1 mm) melanoma[3]. Men over the age of 60 benefited even more, with four times the odds of having a thinner tumour.

ROUTINE CHECKS

The most compelling population-based data are from a skin screening programme in the German state of Schleswig Holstein in which almost 20% of the adult population over the age of 20 — more than 360,000 people — were screened during a one-year period in 2003 and 2004. Five years later, melanoma mortality had declined by nearly 50% compared with surrounding states[4]. The results convinced Germany to roll out the programme nationwide to all adults aged 35 and older in 2008. So far, nearly 30 million screenings have been done, and data on the programme's effectiveness should soon be available.

These studies suggest that routine skin examination by primary-care doctors may be a practical strategy for reducing mortality from skin cancer. The USPSTF is reconsidering its recommendations and calling for a systematic review of current screening practices.

But for now, routine skin examination is far from the norm in the United States. Only 8–21% of people receive an annual skin exam from their doctor, even though primary-care physicians find more melanomas than do dermatologists. Americans make 1.7 visits to the doctor each year on average, and elderly people, who are at greatest risk of fatal melanoma, make many more. So primary-care providers could be an important source of skin-cancer diagnosis and triage.

It should be possible to incorporate screening into the primary-care workflow. It would take a trained physician only a few minutes, as part of a routine physical exam, and could reveal melanomas in high-risk areas not easily viewed by the patient, such as the back. Not all doctors are trained to identify early skin cancer, however. A 1.5-hour, web-based scheme called INFORMED (Internet Curriculum For Melanoma Early Detection) provides training and clinical guidance for the early detection of melanoma and other common skin cancers by primary-care providers. Preliminary data from the two integrated health-care systems that have used INFORMED suggest that it improved the ability of doctors to recognize both benign and malignant skin lesions, and that it also decreased dermatology referrals, particularly to assess benign skin lesions.

THE GROWING BODY OF **EVIDENCE** SEEMS TO TIP THE SCALES IN FAVOUR OF USING **SCREENING** BY PHYSICIANS.

Implementing widespread skin screening requires a shift in the way that primary care is delivered, however, as routine physical examinations are becoming less common. In the present atmosphere of cost-cutting, recommendations from the USPSTF and greater consensus from other organizations are crucial to ensure that patients receive appropriate screening for melanoma. In the interest of reducing deaths from melanoma, the USPSTF should consider all the recent data from worldwide screening efforts.

The growing body of evidence seems to tip the scales in favour of using screening by physicians for melanoma, but there are questions over how to do it. Who should perform, receive and pay for the screens? Training ancillary health-care providers (such as nurse practitioners and physician assistants) could be beneficial, as well as compensating for carrying out full-body skin exams during routine medical visits. Preliminary data from Germany suggest that screening can save lives, but other studies are needed to understand the possible harms of skin screening, along with potential cost savings for the health system. These will vary from country to country but must be understood if skin screening is to be widely incorporated into primary care. ■

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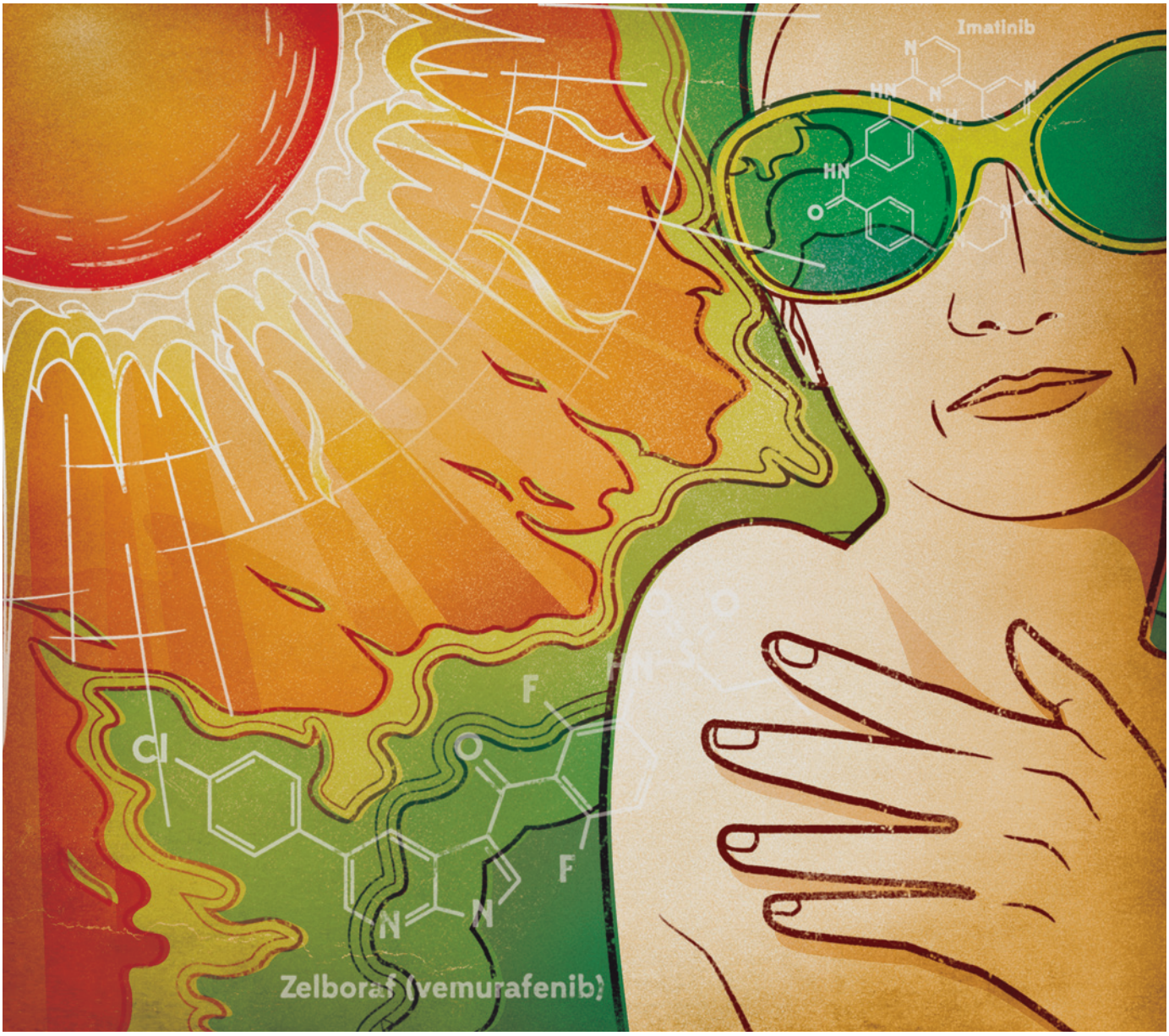


SUSAN BURGHART

DRUG DEVELOPMENT

A chance of survival

People with advanced melanoma are living longer thanks to treatments that target cancerous cells or encourage the immune system to wipe out the tumour.

BY HANNAH HOAG

When Antoni Ribas began treating metastatic melanoma 15 years ago, he faced a lot of difficult conversations with his patients. Few treatments were available for those in the advanced stages of the disease, and none was particularly effective. Patients with stage IV melanoma, which has spread to the lymph nodes or other organs, had a median survival of just 8–9 months, and only 15% lived for more than 3 years[1].

"I would sit down in front of them and discuss treatments that might work for 10% of them at most," says Ribas, a medical oncologist at the University of California, Los Angeles. "And I'd say, it probably won't make a difference if we do treatment or not."

But things have started to change in melanoma care. Since 2011, the US Food and Drug Administration (FDA) has approved seven treatments for advanced melanoma (see 'Treatment of BRAF-mutant melanoma'), including one in September that promotes an immune response against the cancer, and several more are working their way through the process. Drug companies have dozens of treatments in clinical trials.

Targeted therapies, which are tailored to a patient's genetic make-up and are designed to

disable the cancerous cells, have become the cornerstone for the treatment of advanced melanoma. And drugs that target the immune system and enhance its ability to wipe out cancer cells have just entered the clinic. Patients who had once failed to respond to the meagre range of available drugs are now showing strong, long-lasting responses. "It is an amazing thing," says Ribas.

HITTING THE TARGET

For many years, cancer was treated according to the organ in which it developed, or by bombarding it with chemicals that killed off rapidly dividing cells. But then researchers began discovering the genetic mutations that transform a normal cell into a cancerous one. These findings uncovered mutant proteins that could be blocked by new drugs, allowing oncologists to selectively target the tumour.

In the late 1990s, oncologists were excited about a new drug called imatinib (Gleevec) that homed in on the cancer cells of patients with chronic myelogenous leukaemia (CML). Most of these patients have an abnormal gene rearrangement that produces a protein that drives the cancer. In theory, drugs that target this protein should cause the cancer to retreat.

This approach was not limited to leukaemia. Another targeted therapy, Herceptin, was shrinking tumours in an aggressive form of breast cancer characterized by mutations in the *HER2* gene[2]. Such successes left cancer researchers looking for similar mutations that push cells to develop into melanoma.

"When I first saw that paper it stopped me in my tracks."

In 2002, researchers working on the Cancer Genome Project at the Wellcome Trust Sanger Institute near Cambridge, UK, uncovered one of melanoma's weak points. They found that two-thirds of melanomas have a tiny change in the gene encoding a protein called BRAF that is part of a signalling pathway in the cell. The mutation changes one amino acid in the protein[3], altering the pathway so that the cells multiply without limit[4]. "When I first saw that paper, it stopped me in my tracks," says Keith Flaherty, an oncologist at Massachusetts General Hospital in Boston. Identifying the role of BRAF made it possible for the first time to develop "a treatment concept for melanoma", he says.

But it would be years before a promising drug became available. Jeff Sosman, a medical oncologist at Vanderbilt University Medical Center in Nashville, Tennessee, explains: "Until 2008, we honestly didn't know if BRAF was targetable, and if by inhibiting this enzyme we would have an effective therapy," he says. That year, clinics began testing a drug called vemurafenib (Zelboraf), which targets the mutant BRAF. About half of patients with advanced melanoma have a mutation in this protein, known as BRAF (V600E), and vemurafenib was their first chance at personalized medicine.

The results exceeded all expectations. Tumours regressed rapidly and some patients improved overnight. In 2010, a small phase I trial of vemurafenib showed complete or partial tumour regression in 26 of the 32 patients[5]. The response was greater than anything previously seen with advanced melanoma[4]. In a phase III study, Paul Chapman, a specialist in metastatic melanoma at the Memorial Sloan Kettering Cancer Center in New York, showed that after three months of vemurafenib therapy, patients with the BRAF (V600E) mutation were 74% less likely to die or see their cancer worsen than patients who received a standard chemotherapy agent[6]. And 48% of them saw the growth of their tumours shrink or stop.

The FDA fast-tracked the approval of vemurafenib for use in people with the BRAF (V600E) mutation in 2011, less than four months after it was submitted. A second BRAF inhibitor, called dabrafenib (Tafinlar), was given FDA approval in 2013.

FACING RESISTANCE

But cancer is a wily foe. Tumour cells mutate, and when a pathway is blocked, they find another route. So targeted therapies quickly lose their effectiveness, and many people who took vemurafenib found that resistance developed within six months. The tumours, which had once melted away, grew back with new mutations that were impervious to the drug[7].

Other proteins in the same signalling pathway quickly became targets for drug discovery. BRAF inhibitors block the MAPK pathway, and scientists soon realized that most of the resistance comes from reactivation of the pathway through mutations in other genes that play a part in it[7]. The identification of these genes led to the development of more drugs that target the pathway, including MEK inhibitors, such as trametinib (Mekinist), which became the second major player in the treatment of advanced melanoma.

Oncologists then combined anti-BRAF and anti-MEK drugs with the aim of preventing the development of resistance. With the pathway effectively blocked at two points, the tumour cells struggled to develop new mutations. In a small trial of the two drugs, Ribas and colleagues found that more than 85% of patients with a BRAF (V600) mutation who had never received a BRAF inhibitor responded to the combination of drugs, compared with only 15% of those who had developed BRAF resistance during an earlier treatment[8]. Patients who had never taken a BRAF inhibitor lived for 13.7 months before the disease progressed, compared with 2.8 months for those who had previously developed resistance to vemurafenib. In July 2014, GlaxoSmithKline stopped a combined phase III trial of trametinib and dabrafenib early because the drugs had obtained increased survival ahead of its target. "We now have two winning strategies," says Caroline Robert, head of dermatology at the Institut Gustave-Roussy in Paris.

But *BRAF* is not the only important driver mutation in melanoma. Another mutation, in the *NRAS* gene, is found in approximately 20% of metastatic melanoma patients. Drug companies have struggled to find compounds that effectively target the mutated NRAS protein, however, so they have focused instead on the pathways NRAS activates, including MAPK. Indeed, says Sosman, inhibiting MAPK "is probably not enough, but it needs to be a component in the strategy".

In July 2014, French researchers reported another mechanism of resistance to targeted therapies for melanoma[9]. They identified a cluster of proteins called eIF4F, which regulates protein synthesis. Tumours that respond to anti-BRAF drugs have low levels of eIF4F, and those that have developed resistance to these drugs have more. "Understanding this nexus is critical to overcoming resistance to cancer therapy," says Robert, one of the study's authors. The team has identified compounds that inhibit eIF4F and enhance the effectiveness of vemurafenib in mice with melanomas.

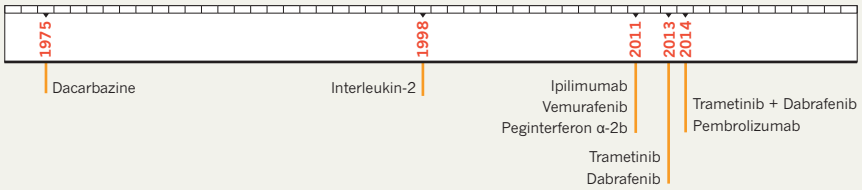
"It's an interesting target downstream of many mechanisms of resistance to BRAF," says Sosman, "and it's exciting that a potential drug might be able to inhibit this effect."

IMMUNE RESPONSE

Long before targeted therapies were possible, biomedical researchers had tried using the immune system to fight cancer. In the 1990s,

TREATMENT OF BRAF-MUTANT MELANOMA

Before 2011, few treatments were available for patients with advanced melanoma. Drugs gave a median survival of 8–9 months and only 15% of people lived for more than 3 years. But in the past four years, the US Food and Drug Administration has approved seven treatments that target the cancerous cells or trigger the immune system to do so, extending patients' lives.



instead of applying an accelerator to the immune system, they tried lifting the brakes by blocking the action of a protein called CTLA-4, which keeps the immune system's T cells in check. CTLA-4 normally has a beneficial role in preventing the immune system from attacking normal tissue. But it is such an effective brake that it also stops T cells from destroying cancer cells. In 1996, a team led by James Allison, now at the University of Texas MD Anderson Cancer Center in Houston, showed that injecting mice with an antibody that blocks CTLA-4 could inhibit tumour growth[10].

These findings eventually led to the development of the drug ipilimumab (Yervoy), a monoclonal antibody that acts as a 'checkpoint inhibitor' by binding to the CTLA-4 protein and stopping it from applying the brake. Ipilimumab was the first drug to extend the lives of patients with metastatic disease[11]. In a large phase III trial of 676 patients with late-stage melanoma, those given ipilimumab survived on average for 10 months[12] — almost 4 months longer than those given another experimental treatment. The FDA approved ipilimumab for the treatment of metastatic melanoma in 2011.

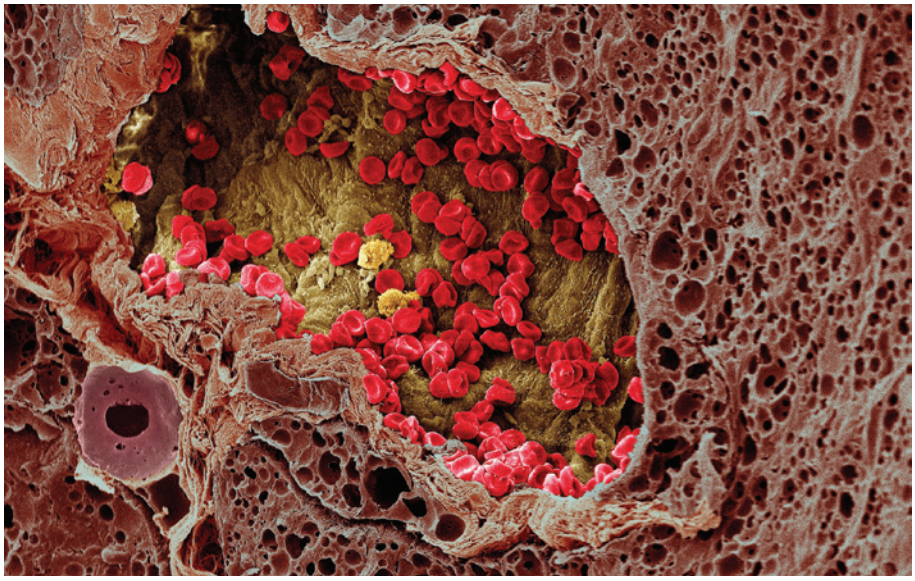
In 2013, a follow-up analysis of 12 studies involving more than 1,800 patients given ipilimumab showed that 22% of patients survived for 3 years or longer, and some were approaching 10 years. Checkpoint inhibitors represent "a paradigm shift, probably the most important discovery in the field", says Ribas.

The trouble with ipilimumab is its toxicity. Releasing the brake on T cells enables them to attack not only cancer, but also normal cells in the skin, colon, endocrine system, eye and elsewhere, says Sosman, who conducted some of the ipilimumab studies. Using the drug requires vigilance from hospital staff to manage the side effects, and patients may be given steroids or even have the treatment discontinued, depending on the severity of the side effects.

Researchers have identified several other checkpoint inhibitors that also release the brake holding back T cells, but with less toxicity. Patients with metastatic melanoma often have high levels of a protein called PD-L1. When PD-L1 binds to a protein called PD-1, which is expressed on T cells, it allows cancer cells to hide from the immune system. Studies have shown that drugs that target these two proteins can shrink tumours.

Ribas and Robert recently led trials that used an antibody called pembrolizumab (also known as MK-3475) to target PD-1. The tumours shrank or disappeared in 52% of patients with metastatic melanoma who received the drug[13]. Another study[14] found that pembrolizumab could slow tumour growth in patients who had stopped responding to drugs that target CTLA-4. Nearly 90% of those who responded to the drug saw their tumours shrink or disappear in six months.

"We see patients who have large, bulky melanomas, tumours that two or three years ago if they said they didn't want to be treated, I would have said OK," says Ribas. "But with this antibody that releases the PD-1 brake, all of a sudden their tumours start melting away with limited side effects."



S. GSCHMEISSNER, K. HODIVALA-DILKE & M. STONE, WELLCOME IMAGES

Scanning electron micrograph showing a blood vessel providing red blood cells (red) to a melanoma.

The FDA approved pembrolizumab (Keytruda) in September 2014. This is the first drug targeting PD-1 or PD-L1 to be approved in the United States, although Japan had already approved the anti-PD-1 drug nivolumab (Opdivo) in July. Anti-PD-1 drugs have been developed at a phenomenal speed, taking just three years from the first clinical trials to approval, says Ribas.

BETTER TOGETHER

Now that targeted drugs and immunotherapy have been established, the next development may be a combination of the two. Doctors can examine a tumour's biological traits and pick the best antibody or combination of drugs to attack it. For example, says Ribas, PD-L1 may be an important biological marker that will enable oncologists to identify patients who will respond best to pembrolizumab. In a large ongoing phase I study, almost half of the PD-L1-positive patients responded to pembrolizumab treatment, compared with only 13% of patients with PD-L1-negative tumours.

Drug companies are enthusiastic about immunotherapy because these drugs seem to be beneficial in several different types of cancer. Many of these checkpoint inhibitors are being tested in other cancers[1], including renal cell carcinoma, lymphomas, lung cancer and breast cancer. Although a smaller fraction of these patients respond to immunotherapy, the responses seem to last longer.

Ultimately, oncologists aim to combine the two treatments to produce a more potent effect. Using CTLA-4 and PD-1 inhibitors together could further boost T-cell activity by releasing the brake at several points during the T cell's interaction with melanoma cells.

But combining targeted therapy with immune therapy might be even more powerful. Targeted drugs could wipe out one type of cancer cell and force it to adjust by developing new mutations. This would expose them to T cells that have had their brakes released to finish the job.

Today's therapies cannot help everyone with advanced melanoma, but physicians now have a choice of drugs to target different forms of melanoma, and researchers are developing the tools to match patients to specific treatments. "After more years of doom and gloom than I'd care to count, we've had this amazing trajectory that doesn't seem done yet," says Flaherty. "Our confidence keeps rising as our patients keep surviving." ■

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MIKE BRADLEY

Jackie Smith survived melanoma but not enough is known about what causes the disease in black people.

SKIN COLOUR

No hiding in the dark

Melanoma is most common in light-skinned people, but it can also afflict those with darker pigment. Finding out why would help to explain the disease's origins.

BY SUJATA GUPTA

When Jacqueline 'Jackie' Smith was 19, she spotted a large, irregular mole along the right side of her bikini line. Concerned, she went to the doctor and had it removed. The biopsy results came back normal, but a few years later, a hard, almond-sized growth appeared in the same area. "If I had stretch pants on you could see the lump," says Smith, a doctoral student in sociology at Syracuse University in New York. Doctors thought it was an infection and put her on antibiotics. Yet the lump remained.

A couple of years later, Smith went to the doctor again to have the lump removed. This time, the biopsy led to a diagnosis of melanoma. The lump was a lymph node filled with cancerous cells. "I was told it would be a miracle if I lived another 5 years," she says.

Smith would just be another melanoma statistic except she stands out in an important way: she's black. Melanoma rates have jumped in white people over the past 30 years, but they have stayed flat in people of colour. A white person in the United States has a 1 in 50 chance of developing melanoma, compared with just a 1 in a 1,000 chance for a black person.

Darker skin contains more melanin, a pigment that protects against ultraviolet rays. Most melanomas in white people can be linked to mutations caused by sun exposure[1], whereas at least half of melanomas in black people occur on areas not exposed to the sun[2]. But although melanoma in dark-skinned people is rare, it's highly lethal. The five-year survival rate of an African American diagnosed with melanoma is 73% compared with 91% in Caucasians.

Most melanoma research is done on white people, so the reasons for this disparity are unknown. Researchers still don't know what causes melanoma in people with dark skin. As a result, it is unclear whether treatment should differ according to skin colour, or whether prevention messages that focus on sun protection are appropriate for black people. Part of the problem is designing a study that classifies people by skin colour. The usual ethnic groupings, such as Hispanic, don't work because some Hispanic people have pale skin, whereas others are dark. "To put them all into one basket and to treat them as one risk group is silly," says Dennis Hughes, a paediatric oncologist at the MD Anderson Cancer Center in Houston, Texas. "But that is exactly what we do."

A WHITER SHADE OF PALE

The humans who originated under the hot African sun some 200,000 years ago were almost certainly very dark — the melanin was

MICHAEL OCHS ARCHIVES/CORBIS

Bob Marley died from a brain tumour that arose from acral melanoma in his big toe.

a natural sunblock that prevented the sun's ultraviolet rays from penetrating deep into the body and causing radiation damage. But it meant they needed to spend considerable time outdoors being exposed to the sun to synthesize enough vitamin D, which protects against osteoporosis and could help to prevent autoimmune and inflammatory diseases. But as humans began migrating out of Africa to dingier climes in East Asia and Europe, their skin gradually lightened — a change that led to more rapid vitamin D synthesis, but increased the risk of skin cancer.

Some of these changes in pigmentation can be traced to mutations in the *MC1R* gene, which encodes a protein called melanocortin 1 receptor that controls the type of melanin synthesized in the skin. When the protein is active, it produces a dark pigment known as eumelanin that provides sun protection and helps with DNA repair. But mutations in the gene inactivate the protein, so the body produces pheomelanin, which is abundant in people with fair skin, freckles and red hair. People of all colours produce both types of melanin, just not in the same quantities.

"Acral and mucosal melanomas clearly have a different biology to those linked to sun exposure."

Spending time in the sun prompts the skin to synthesize new melanin. For those with skin rich in eumelanin, this typically results in a tan. But for many pheomelanin-rich white people, burning and blistering is more common — and the risk of melanoma jumps for every blistering sunburn experienced during childhood[3].

But pheomelanin can cause cancer even in the absence of ultraviolet light, says David Fisher, director of the melanoma programme at the Massachusetts General Hospital Cancer Center in Boston. He has shown that mice bred with the equivalent of red hair and fair skin develop melanomas at much higher rates than 'black' and albino mice (which lack melanin altogether). So although people with dark skin produce this dangerous melanin in much lower quantities than white people, it could explain why they still occasionally develop skin cancers, Fisher says.

BOB MARLEY'S BIG TOE

In the summer of 1977, Jamaican reggae singer Bob Marley was playing soccer in France when he injured his right big toe. When the wound festered, a doctor removed the toenail. Then Marley re-injured the toe during another soccer game. A new wound appeared. Marley went to see another doctor who, shocked by the toe's atrophied appearance, conducted a biopsy and diagnosed Marley with melanoma. The doctor advised amputating the toe to prevent the cancer from spreading, but Marley refused on religious grounds. The cancer spread, and in 1981, just four years after the initial injury, the dark-skinned singer died of a brain tumour. He was 36.

Marley had acral melanoma, a subtype that appears on the palms and soles of the feet, and under the nails — areas that have little or no sun exposure. Related melanomas can appear inside mucous cavities, such as the vagina or the mouth. Fewer than 5% of melanomas are acral or mucosal, but they account for more than half the melanomas found in black people[2]. That's because dark-skinned individuals are less susceptible to melanomas related to ultraviolet light, so a greater proportion of their melanomas have nothing to do with the sun.

Acral and mucosal melanomas "clearly have a different biology" to those linked to sun exposure, says Jeffrey Sosman, an oncologist at Vanderbilt University in Nashville, Tennessee. Scientists now need to work out what causes those melanomas — and how to treat them.

DEVELOPING EARLY

Jackie Smith had her almond-sized lump treated at the Moffitt Cancer Center in Tampa, Florida, which is near her parents' home. Surgeons excised the cancerous lymph nodes and radiated the tumour site, and gave Smith interferon, an immune therapy that requires patients to give themselves regular injections for up to a year. The drugs made Smith feel like she had a bad case of flu. Her teeth chattered constantly and she developed lockjaw from the antinausea medication. She had to put her doctorate on hold.

These days, tumours of patients with advanced-stage melanomas are sometimes genetically sequenced to help determine the best treatment. For instance, 60% of tumours on sun-exposed areas of skin have mutations in the gene *BRAF*, for which targeted drugs are available[4]. But most acral and mucosal melanomas have no known genetic cause, making treatment more difficult.

The immune therapy that Smith received has only become possible in the past decade. Sosman has found that such therapies, which help a patient's immune system to fight the cancer, seem to be most effective in treating melanomas with a high number of genetic mutations — that is, those arising from sun exposure. That makes sense, he says, because mutations probably create abnormal proteins that the immune system recognizes as foreign. But that means immune therapies may be less effective at snuffing out non-sun-related tumours, such as those often found in dark-skinned people like Smith.

It's impossible to know what caused Smith's cancer or why her treatment worked, especially as her tumour was not sequenced. Sun exposure could be a culprit, as Smith, despite her dark skin, is prone to burning. But her surgeon at Moffitt, Vernon Sondak, suggests another possibility. He wasn't able to determine the primary site of Smith's tumour, but he thinks it may have arisen from the odd-looking mole she had removed when she was 19. That fits with data showing that melanomas have been rising in children and teens.

The rise is greatest in white teenage girls, as these are frequent users of sunbeds, but a slower rise has also been observed in younger children. Although fewer than 5% of melanomas in the United States appear in adults with dark skin, the figure is much higher in children. One study found that almost 18% of melanoma patients aged between 1 and 4 were non-white[5]. The implications for Smith's case are clear. "Maybe this is something that started when she was much, much younger and just took many years to show up," Sondak says.

DELAYED DIAGNOSIS

Now, seven years after her diagnosis, Smith is just a few months away from finally completing her doctorate. Life has almost returned to normal. But partly because of her late diagnosis,

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she still suffers from some problems. She has periodic swelling, called lymphoedema, in her right leg, caused by the removal of the lymph nodes in her groin. She has to wear a compression stocking, and wearing heels can be difficult because her feet swell.

Such late-stage diagnoses are common in people of colour. In 2006, when Robert Kirsner, head of dermatology at the University of Miami's Miller School of Medicine, compared the stage of diagnosis among nearly 1,700 white, black and Hispanic patients in Miami-Dade County in Florida, he found something troubling. Only 16% of whites were diagnosed after the tumour had begun to metastasize, but that jumped to 26% in Hispanics and 52% in blacks[6] — a pattern Kirsner says could explain the higher mortality rates from melanoma among minorities. His subsequent work suggests that the delays in diagnosis may be socioeconomic or related to inadequate public-health campaigns. Patients and clinicians often don't even realize that dark-skinned people can get melanoma, he says.

To address this disparity, the American Academy of Dermatology (AAD) convened a working group of skin-colour specialists and issued fresh guidelines earlier this year[7]. They suggested that all non-Caucasians conduct a thorough skin exam once a month, paying special attention to the palms of the hands, the soles of the feet, under the nails, and body cavities. They also reminded people of colour to follow the same stringent sun safety measures as white people: seek shade whenever possible, wear protective clothing and hats, apply sunscreen regularly, and avoid sunbeds. "Even though their risk is lower than very fair-skinned Caucasians, it's not zero," says Henry Lim of the Henry Ford Hospital in Detroit, Michigan, who led the AAD group.

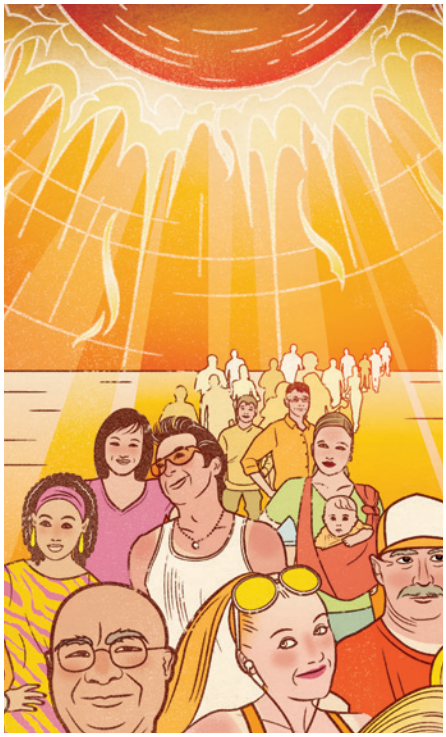
"The melanoma risk for black people is lower than for fair-skinned Caucasians, but it's not zero."

COLOURING THE ADVICE

Will such stringent guidelines lower melanoma rates in people with dark skin and help reduce the ethnic disparities in health outcomes? Research and prevention messages for melanoma are based almost exclusively on whites, so it's not at all clear.

The problem starts with the basics, Kirsner says. The standard self-examination instructions tell people to look out for moles that are asymmetric, have irregular borders, are unevenly coloured, are larger than 6 mm in diameter, or are changing. But these guidelines, says Kirsner, "are based on white people". Cancerous moles on dark skin may look different, he explains.

What's more, studies of melanoma in people of colour have largely focused on ethnicity, rather than skin colour. Giving advice to 'Hispanics', 'African Americans' or 'Asians' doesn't make much sense because someone's ethnicity says little about their skin colour, which is the main determinant of melanoma risk, says Nina Jablonski, an anthropologist at Pennsylvania State University in University Park, who



specializes in the evolution of skin colour. Yet this is precisely what happens. The AAD report[7], for instance, defined Caucasians as "non-Hispanic individuals of European descent". Everyone else — from lightly pigmented Asians and Asian Indians to Africans — were lumped together as "people of colour". "That's a tremendously heterogeneous group," Jablonski says.

There is little doubt that advising a fair-skinned redhead to treat the sun as a carcinogen is scientifically sound, but it's less clear for people of colour. Given the rarity of melanomas in dark-skinned individuals, coupled with their high proportion of acral or mucosal melanomas, the odds of them developing melanoma from excessive sun exposure are slim. "Do we need to give them the same photo-protection advice?" asks Lim. "Probably not." The challenge, he says, is coming up with personalized guidelines that are easy to follow — but this could take several years, so the message will remain the same for now.

Australia and some European countries have already personalized skin protection advice based on skin colour, however. Dark-skinned individuals are generally told that limited sun exposure is fine, even healthy, as it promotes vitamin D synthesis. In the United States, dark-skinned people are advised to take vitamin D supplements instead.

Education and outreach may be unable to help much too. When dark-skinned individuals and white people present with tumours of the same size, the melanoma in the person with dark skin is more likely to have metastasized. This suggests that people with dark skin may be predisposed to more severe forms of melanoma[8], making early detection difficult.

The first step to understanding what's going on, says Esteban Parra, a molecular anthropologist at the University of Toronto in Canada, is to measure skin colour objectively[9]. These quantitative skin colour scores could then be matched to tumour sequencing studies to distinguish between genetic variants that increase skin-cancer risk by altering pigmentation and variants that increase risk but have no bearing on pigmentation.

Parra points to a pair of studies that exemplify this approach. Researchers looked at 12 variants in 4 genes known to be involved in pigmentation to determine if and how those genes altered skin colour in Japanese people. The researchers assessed pigmentation by using a spectrophotometer, which measures the reflectance of skin, and found that variants of a gene known as *OCA2* lightened skin colour[10].

This year, the same researchers found that these skin-lightening variants also increased the likelihood of developing skin cancer[11], enabling them to draw a clear line from genetic variation to skin colour to cancer risk. "It will be fantastic if more people start including quantitative measures of pigmentation in their research," Parra says.

Until then, the best advice is for people of all colours to get to know their skin, and to have it checked if they see something amiss. Jackie Smith credits her doggedness for saving her life. "We all have this sense about something not being right," she says. "I had that sense but I was also really happy when the doctor said, 'Oh this is nothing to worry about'." But she still felt uneasy and went back to the doctor, and it paid off. "I'm still here," she says. ■

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PROTECTION

The sunscreen pill

A tablet that protects against sunburn is an attractive idea, but the science is patchy.

BY ERIN BIBA

It sounds like a lazy sunbather's dream come true: a pill that has all the protective properties of sunscreen without the bother of slathering yourself in lotion or remembering to re-apply it. Over the years, research into such a pill[1] has yielded a slew of over-the-counter supplements that claim to fight sun damage to the skin, mostly based on the fact that they contain antioxidants. But the US Food and Drug Administration (FDA) doesn't regulate supplements, so none of these products have needed to prove their effectiveness. Despite much research and a plethora of claims by manufacturers, the problems of moving antioxidants through the human body make it tricky to develop a pill that can replace sunscreen lotion.

Many of the current pills are based on an antioxidant-rich extract from the tropical fern *Polypodium leucotomos*, although a UK researcher is trying to patent an extract from algae found on coral. And there are reasons to suppose that antioxidants might help. Exposing the skin to ultraviolet radiation triggers the formation of certain reactive oxygen species known as free radicals that damage skin cells and can ultimately lead to malignancy. Antioxidants are known to destroy free radicals in the body and on the skin. The hard part is getting the antioxidants from the stomach to the skin.

Salvador González, a dermatologist based in Madrid, Spain, who works as a consultant with the Memorial Sloan Kettering Cancer Center in New York, has been studying the fern extract since the early 1990s. But making it work effectively in pill form is difficult, he says.

LESS RADICAL

Scientists have tested the extract against various diseases and disorders such as skin cancer. They have injected it, applied it topically to the skin, and given it to patients in pill form. All these methods revealed at least some reduction in the amount of free radicals on the skin[2]. But pills were the least beneficial route, largely because of the way the body's metabolism interacts with the extract.

"If you think about taking a pill by mouth, it has to go through multiple steps," explains Henry Lim, a dermatologist at the Henry Ford Hospital in Detroit, Michigan. "It has to be absorbed, go through the blood and then through the liver before it gets to the skin." This is especially problematic for an antioxidant-based sunscreen pill because antioxidants, by their very nature, are unstable and tend to break down before they reach the target.

There is some evidence that antioxidants do reach the skin, however. A small 2004 study in which people were given oral doses of the fern extract after exposure to ultraviolet light found that their skin was less red and had fewer sunburnt cells than subjects not given the extract[3,4]. And a 1997 study looked for markers of cell damage caused by exposure to ultraviolet light in ten volunteers who ingested the fern extract[5]. The extract boosted the ability of the immune system to repair the damage caused by sunlight, and reduced the reaction of the skin cells to ultraviolet that results in sunburn. They also exposed subjects to twice the threshold of ultraviolet needed to cause sunburn and found that damage in those given the fern extract decreased by 84%, whereas it increased by 217% in subjects not given the extract. The results were not statistically significant, but the researchers suggested that larger studies may

show that the fern extract protects the skin.

Despite these data, Lim — who has worked as a consultant to Ferndale Healthcare, a supplement manufacturer in Detroit that makes a fern-based sunscreen pill — says no dermatologist would currently recommend using a pill instead of sun lotion. "None of the pills at this moment are 100% successful," he says.

LOOSE REGULATION

One problem in assessing the pills currently on the market is that they are deemed to be supplements, not medicines, so they are not regulated by the FDA. As long as the manufacturer makes no false or misleading claims, and there is no immediate health threat, the makers can sell whatever supplements they want — it's up to the consumer to decide whether they are worthwhile or not.

In the United States, supplements are regulated more loosely than sunscreen lotion, which is viewed as both a cosmetic and a drug. Cosmetics are regarded as anything that is applied to the body for cleansing or beautifying, and a drug is something intended for treatment or prevention. Because sunscreen lotion is both, it must follow the regulations for each type of product. Cosmetics don't require FDA approval, but drugs do, so sunscreen lotion is held to a higher standard than normal moisturizer — and also higher than supplements.

In August 2013, the American Academy of Dermatology released a statement on oral sunscreens declaring that there is "no scientific evidence that oral supplements alone can provide an adequate level of protection from the sun's damaging ultraviolet rays."

Dermatologists say that a pill may well be a reasonable addition to a cream-based sun protection regimen, which should also include wearing long clothing and a hat, and staying in the shade. In a series of studies González has conducted over the years, he was able to achieve a sun protection factor (SPF) of just 2 from the fern-based pill, compared with SPFs ranging from 15 to 50 for sun creams on the market in the United States. "Increasing the amount of antioxidants in a pill to a level that could robustly block sun damage would probably cause unwanted side effects," he says.

MAKE TAN

The most promising example of a non-topical sunscreen is a prescription drug created by the company Clinuvel Pharmaceuticals based in Melbourne, Australia. Known as Scenesse (afamelanotide), and currently awaiting FDA approval for marketing in the United States, it is a chemical analogue of a naturally occurring hormone, α-melanocyte-stimulating hormone, that is released into the body on exposure to ultraviolet radiation. The hormone — and the drug — triggers skin cells to release the dark pigment melanin, as they do to create a tan when skin is exposed to the sun.

Tanning creates a natural shield against ultraviolet radiation. The melanin acts as a filter, screening out some of the wavelengths of sunlight that induce the formation of dangerous free radicals. Lim, who consulted with Clinuvel while they were developing the drug, says that anyone who takes Scenesse would eventually become very tanned and, as a result, would be much less likely to burn.

But Scenesse is not marketed at general consumers — the FDA approval would be for use as a prescription drug to treat people with diseases such as vitiligo that make them extremely photosensitive. Clinuvel hopes the drug can also be used to treat people with photodermatosis, a disorder that causes mild-to-severe skin rashes after exposure to ultraviolet radiation.

If approved, Scenesse will not be administered as an oral pill, but as an implant the size of a grain of rice that is injected under the skin. Tanning from the injection will start within two days and lasts up to two months before another injection is needed. However, because it is injected, and is only indicated for severe photosensitivity disorders, it is impractical as an everyday treatment for people who lack sun-sensitivity diseases. The injection would protect patients from severe sun damage, but Clinuvel actively discourages people from thinking of the drug as a sunscreen pill.

Another lead in the search for a pill to prevent sun damage comes from Paul Long's lab at King's College London — and it's based on compounds made by algae that live on coral. Over the past five years, Long has been studying mycosporine-like amino acids (MAAs), which are naturally occurring sunscreens produced by organisms that live in clear, shallow water and so are exposed to high levels of ultraviolet radiation. Long discovered that the algae living inside coral produce MAAs and pass them to the coral they live on. Both organisms, and the fish that eventually feed on them, are protected by the MAAs, which absorb ultraviolet radiation before it can damage them. By sequencing the coral's genome, Long identified the genes that encode the pathway that allows the coral to take up and use the MAAs.

Long is trying to patent the ingredient for use in pills, but it's already proving effective in other products. In 2012, King's College London entered into partnership with Aethic, a UK skincare company, to commercialize the use of MAAs in sunscreen lotions.

González says the research is promising but that MAAs will be one of many sun-protective compounds derived from nature, none of which is fully effective in blocking the sun. So in the end, any sun-protection regimen will still have to include lotion and a good hat. ■

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PERSPECTIVE

Protect the USA from UVA

The United States does not have access to the latest sunscreens. The Sunscreen Innovation Act could set that right, says **Michael J. Werner**.

According to the Skin Cancer Foundation, more than 3.5 million skin cancers and 76,000 melanomas are diagnosed each year in the United States, and, on average, one person dies from melanoma every hour. As with most diseases, the best way to fight melanoma is to prevent it. Unfortunately, the latest sunscreen ingredients that can help to reduce the risk of melanoma and other skin cancers have languished for decades awaiting approval from the US Food and Drug Administration (FDA).

The ultraviolet (UV) filters in sunscreen work by absorbing, reflecting or scattering the UV light emitted by the Sun. UVA radiation, which represents roughly 90% of UV radiation, can accelerate skin ageing, cause skin damage and create a risk of skin cancer by damaging DNA. The other component, UVB, leads to sunburn and also increases the risk of skin cancer. The most effective protection blocks both UVA and UVB. But ingredients delayed by the FDA approval process would provide additional options, especially for UVA protection.

The active ingredients used in sunscreens are regulated by the FDA as drugs. But the FDA has not approved an over-the-counter sunscreen ingredient since 1999. In 2002, it created a new pathway to market for non-prescription ingredients, such as sunscreens, that allowed manufacturers to use data from other countries to establish that a product is safe and effective. To qualify for this 'time and extent application' (TEA) process, the company must establish that a product is approved in at least one comparable country and that it has been in use for at least five years in sufficient quantity. The TEA process was designed to streamline the review of new ingredients, and the FDA said that it expected to complete the evaluation of sunscreen ingredients within 90–180 days.

THE FDA HAS NOT **APPROVED** AN OVER-THE-COUNTER SUNSCREEN INGREDIENT SINCE **1999.**

SLOW PROGRESS

Unfortunately, it has not gone according to plan. After more than 12 years, the FDA has still not approved a single sunscreen ingredient through the TEA process. This means that Americans still lag behind the rest of the world regarding access to the latest UVA filters — even though these ingredients now have a long history of safe use in Europe, Australia and other parts of the world.

There are currently eight ingredients waiting for a decision from the FDA, some of which were submitted for approval as long ago as 2002. Bemotrizinol, for example, has been languishing in the TEA queue since 2005, despite being approved for use in the European Union (EU) in 2000.

In the past few months, some manufacturers have received letters in response to their applications, but for many this was the first feedback they had received. In the letters, the FDA consistently argues that the products must undergo additional safety testing.

The FDA seems to be backtracking on the TEA process. At a recent meeting of its Nonprescription Drugs Advisory Committee about pending sunscreen ingredients, the FDA argued that the approval in a comparable jurisdiction, such as the EU, and experience of safe marketing is insufficient to support the approval of a sunscreen ingredient in the United States. Rather, the FDA would like companies to perform additional safety testing unique to the United States. This might include studies of dermal safety, 'bioavailability', carcinogenicity, developmental and reproductive toxicity, and toxicokinetics. The FDA acknowledged that some of these tests would take at least two years.

The FDA's sluggish regulatory response prompted the formation of the Public Access to Sunscreens (PASS) Coalition in March 2013, for which I am a policy adviser. The coalition's mission is to work with the FDA, Congress, the White House, health providers and consumer organizations to establish a regulatory pathway for the timely and transparent pre-market review of new, safe and effective sunscreen ingredients. The coalition, which comprises cancer research organizations, academic scientists and sunscreen manufacturers among others, thinks that the FDA should ensure it is adopting a risk-based approach, taking into account the known risk of skin cancer and melanoma, and balancing the benefits of sunscreen protection against the potential risks. Additional testing should be required only if international experience, adverse event reporting, or other scientific information reveals that the product's risk profile demands it.

Efforts by PASS led to the introduction of the Sunscreen Innovation Act in March 2014. The act reforms the TEA process to establish a predictable and transparent process for the review of sunscreen ingredients to ensure that safe and effective products reach the market as soon as possible. It maintains the existing requirements for TEA products but ensures that the FDA's safety and effectiveness review is completed within statutory deadlines in a transparent way, including an opportunity for public comment. The act calls for a formal evaluation of the process and requires reports on the FDA's progress in processing applications to be made available to the public.

The bipartisan act passed the US Senate unanimously in September 2014 and the US House of Representatives unanimously in November 2014. It is expected to be signed by the President later this year.

The PASS coalition continues to fight for the enactment of the Sunscreen Innovation Act and to ensure that safe sunscreens reach the market as soon as possible. This provides a responsible solution to a problem that is exacerbating a public-health crisis. Giving Americans more choices and promoting sunscreen innovation will go a long way towards preventing a deadly disease. ■

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