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 exposure¹, whereas at least half of melanomas in black people occur on areas not exposed to the sun². 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

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.

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 childhood³.

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 people². 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 anti-nausea 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 available⁴. 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-white⁵. 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,

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 blacks⁶ — 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

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

issued fresh guidelines earlier this year⁷. 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.

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 report⁷, 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 melanoma⁸, 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 objectively⁹. 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 colour¹⁰.

This year, the same researchers found that these skin-lightening variants also increased the likelihood of developing skin cancer¹¹, 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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