It's the most common type of cancer in the United States. Nearly two million Americans will be diagnosed with it this year. What's behind the epidemic of basal-cell skin cancers?

THE WAGES OF SUN AND GENES

There's nothing more relaxing than the warm sensation of sunlight on bare skin. It brings back memories of lazy summer days at the beach, baseball games on hot July weekends and stretching out in the backyard to work on a tan.

Not only does being in the sun make us feel good, our youth-oriented society equates bronzed skin with health, fitness and beauty — an attitude that has spawned a multi-billion-dollar indoor tanning industry to provide tanning beds and sun lamps for people who want to get that golden glow without going outside.

BY SALLY POBOJEWSKI

MARK TOMALTY/MASTERFILE

It's true that some exposure to sunlight is important for good health. Sunlight interacts with a hormone in skin cells to trigger the production of vitamin D, which builds strong bones and may help protect against heart disease. Sunshine also eases the symptoms of depression and other mood disorders. But dermatologists say just 10-15 minutes of exposure per day is enough to get the benefits of sunlight, without increasing the risk of skin cancer.

Ultraviolet radiation — either from sunlight or a tanning bed — is the major cause of skin cancer. UV radiation penetrates skin cells and damages DNA, causing genetic mutations that can lead to the development of skin cancer decades later. Occasional severe sunburns in childhood and adolescence can be just as dangerous as continuous long-term sun exposure. Yet, the concept of shielding skin from the sun seems foreign to many Americans. A 2007 survey conducted by the CDC's National Center for Health Statistics found that only 56 percent of adults routinely used sunscreen and wore hats or protective clothing.

The bill for sun obsession in our youth comes due when we get older. With millions of formerly sun-crazed Baby Boomers entering their senior years, dermatologists report they are seeing more patients with skin cancer — mostly basal- and squamous-cell carcinomas — now than ever before.

A recent study of Medicare data found that the number of non-melanoma skin cancer treatment procedures billed to Medicare increased 76.9 percent from 1992 to 2006. Based on these data, researchers estimate that more than 2.1 million Americans were diagnosed with these cancers in 2006.

Sun exposure is only one factor behind the skin cancer epidemic, however. The rest of the story is in our genes. And when it comes to the most common type of skin cancer — basal-cell carcinoma — the most important genes are in the hedgehog pathway.

REGULATING GROWTH AND DEVELOPMENT

Andrzej "Anj" Dlugosz, M.D., the Poth Professor of Cutaneous Oncology, is hedgehog's biggest fan. He has spent more than 13 years trying to figure out how the gene controls the behavior of normal skin cells and cancer cells via a pathway of biological signals. In a human embryo, signals from the hedgehog pathway control cell division and differentiation — for example, turning a limb bud into a fully developed arm and hand with five fingers, with the correct size, shape and placement. After birth, the hedgehog pathway continues to regulate brain and bone development in babies and children. In adults, it controls the growth of hair follicles and may be involved in recovery from injury.

"The best example of hedgehog's role in adult regeneration is the hair follicle," says Dlugosz, professor of dermatology and of cell and developmental biology. "Hair follicles are miniature organs that cycle through periods of growth, regression, and rest during adult life. When the follicle goes into its resting phase and shuts down, the hedgehog pathway is turned off. When the follicle starts growing again, the pathway is turned on. If you block the hedgehog pathway, hair follicles cannot regenerate and produce hair."

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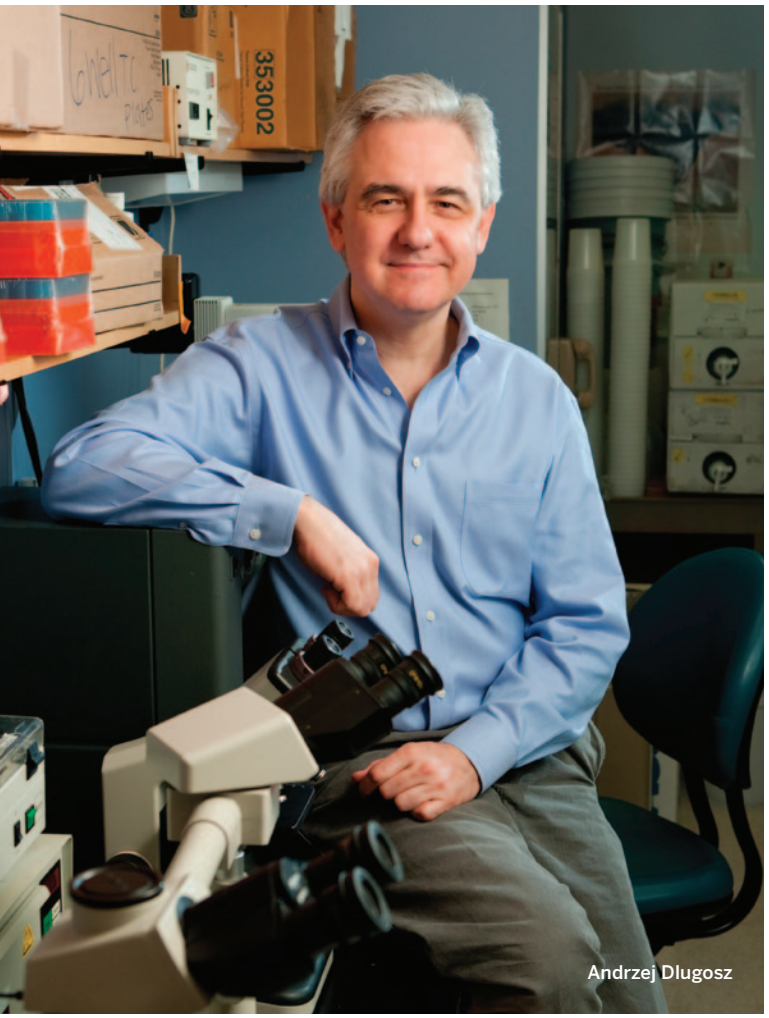
Because the hedgehog pathway is so powerful, it can be dangerous. So the body has evolved many ways to keep unintended hedgehog signals from reaching a cell's DNA where they cause changes in gene expression. One of the most important is a hedgehog receptor molecule called PTCH1. When hedgehog is not present and PTCH1 is working as it should, it blocks a protein called SMO and prevents it from turning on other proteins in the pathway.

"PTCH1 works like the brakes and SMO like the accelerator," says Dlugosz. "In a resting cell, the brakes are on and this prevents activation of the pathway. During development, hedgehog molecules bind and inhibit PTCH1, so the brakes are off and now SMO can activate the pathway. Normally, the hedgehog proteins are made only for a specific period of time, and once they're gone PTCH1 can again block the pathway and the cell goes into a resting state.

"But in cancer, there are either mutations in the PTCH1 gene that make it non-functional, like brakes that aren't working, or mutations in the SMO gene that prevent it



Andrzej Dlugosz

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from being inhibited, like an accelerator that's stuck, or cells start making abnormally large amounts of hedgehog molecules — and they don't stop."

In each case, the result is the same: Uncontrolled hedgehog signaling stimulates abnormal growth of a cell that leads to cancer. If the hedgehog pathway is permanently activated in a developing brain cell, the result is medulloblastoma, a serious pediatric brain cancer, says Dlugosz. When uncontrolled hedgehog signaling occurs in skin cells, it causes basal-cell cancer.

"The critical thing about the hedgehog pathway is that it must be carefully regulated, being turned on and then off at specific times and places throughout the developing embryo and in a few adult organs" says Dlugosz. "In normal cells, hedgehog signaling is tightly controlled. But in basal-cell cancer and some other cancers, it's turned on and it stays on."

So what determines whether a skin cell gives rise to a basal-cell cancer? Why does one patient develop a tumor on his nose, while another patient gets one on her cheek?

"Much of it could be pure chance," Dlugosz says. "Not every cell responds to UV radiation or other DNA-damaging stimuli in the same way, and there are mechanisms in place to repair mutations. Even if cancer-causing hedgehog pathway mutations do occur in many skin cells, it's possible that only some of those cells, possibly just the stem cells, have the long-term growth capacity they would need to become a cancer. It's also possible that potential basal-cell cancer cells may require changes in other signaling pathways that interact with the hedgehog pathway, or signals from surrounding cells that may be needed to initiate and maintain tumor growth. At this point we really don't know all the details, but we do know that uncontrolled hedgehog signaling is a key event in BCC development and is probably required for growth and survival of tumor cells."

EASY TO MISS — OR DISMISS

Unlike melanoma, there's nothing sinister-looking about the early stages of basal-cell cancer. It begins as a small red spot, a raised pink or pearly bump, or a sore that won't heal — usually on the head or face. Assuming it will go away, people often ignore the lesion and wait months or years before they see a doctor and get a biopsy.

Basal-cell cancer occurs four times more often than squamous cell — the second-most common form of skin cancer — and it's most common in people with fair skin, blue or green eyes, and blonde or red hair.

Fortunately, this type of skin cancer grows slowly and rarely spreads to other organs in the body. Low-risk basal-cell cancers, such as superficial tumors on the trunk or extremities, can usually be scraped off and cauterized. High-risk tumors, based on their size, location on the head and neck, or infiltrative growth pattern, are usually removed surgically, often using a specialized procedure called Mohs micrographic surgery that has a five-year cure rate of 99 percent, and is performed at many health centers, including the U-M Comprehensive Cancer Center.

Because it's less aggressive and more easily treated than other skin cancers — such as squamous-cell, melanoma or Merkel cell — it's easy to dismiss BCC as no big deal. But

there's nothing trivial about basal-cell carcinoma. Without treatment, the tumor can spread and be quite destructive, particularly on the face where it can grow into the nose, eye or ear. Although Mohs surgery minimizes the amount of surrounding tissue that needs to be removed, excising the tumor leaves permanent scars, and since BCC is most common on the head or face, the after-effects of treatment are visible and can be disfiguring in advanced cases. Unless every malignant cell is cut out or destroyed, the tumor can grow back and is more difficult to remove the second time.

The risk of developing another basal-cell cancer is 10 times higher for people with a history of BCC than it is for the general population. Even more alarming, a recent study found that the risk for other types of cancer — especially lung, colorectal, breast, prostate and pancreatic cancer — was twice as high in people previously diagnosed with any type of non-melanoma skin cancer than it was for those who never had skin cancer. The association was strongest for adults ages 25-44.

BLOCKING THE PATHWAY

In addition to basal cell cancer, several internal malignancies have abnormally activated hedgehog signaling, so pharmaceutical companies have been aggressively searching for drugs to block the activity of molecules in the hedgehog pathway. The goal is to develop targeted drugs to treat hedgehog-activated tumors, with a response in BCC serving as proof of concept, and with the hope that an oral or topical inhibitor could eliminate BCCs or at least shrink them, making them easier to remove with surgery.

One of the first experimental drugs in clinical trials, a compound called GDC-0449, was developed by scientists at Genentech in collaboration with Curis. The drug inhibits SMO to effectively shut down hedgehog signaling, and the results of a phase I clinical trial in basal-cell cancer published in the September 2009 issue of the *New England Journal of Medicine* were very encouraging. The drug is now being tested as an oral agent in additional clinical trials, at the U-M and elsewhere, in patients with locally advanced or metastatic basal-cell cancer, as well as in patients with breast, colorectal and pancreatic cancer. Later this year, Dlugosz and his colleagues will be participating in a phase II/III study of a topical SMO inhibitor from Novartis.

"If you could use a cream to block the hedgehog pathway and treat basal cell cancer, that could be a great alternative to surgery in selected cases," says Dlugosz. "But there are still many questions to answer. At this point, we don't know if tumors will develop resistance to these drugs or if they leave some residual tumor cells behind, so the cancer could return once the treatment is stopped. This is a real concern because that's what we saw in a mouse model of BCC, where we genetically turned off the hedgehog pathway and tumors regressed, but they quickly grew back when we reactivated the pathway.

"So one possibility for the future would be to first treat with a hedgehog pathway inhibitor to reduce tumor burden, and then go ahead with surgery. We also don't know if shutting down the hedgehog pathway has toxic side-effects, but that should be less of a concern for a topical treatment. So far, some patients have taken the drug orally for over a year without serious side-effects, but it's really too early to know for certain until many more patients are treated."

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There is one side-effect to turning off the hedgehog pathway, which Dlugosz and other researchers predicted based on experiments done several years ago with mice. Since hair follicles need hedgehog signaling to grow new hair shafts, mice taking hedgehog inhibitors lose their hair — something which also has been reported by some patients on the drug in clinical trials.

If clinical trials of hedgehog inhibitors are successful, physicians could have a less-expensive, non-invasive treatment option for some patients with basal-cell skin cancer.

For younger Americans, protecting your skin from UV radiation is still the best way to prevent basal-cell cancer. Use sunscreen. Stay out of tanning beds. Wear a hat. The DNA you save will be your own. [M]

MERKEL CELL CANCER: RARE, BUT DEADLY

On the opposite end of the skin cancer spectrum from basal-cell carcinoma is Merkel cell cancer. While basal-cell is the most common type of skin cancer, Merkel cell is extremely rare. Basal-cell tumors grow slowly and hardly ever metastasize, while Merkel cell is more aggressive than melanoma and has a higher mortality rate.

"Merkel cell was always the orphan disease," says Christopher Bichakjian, M.D. (Residency 2001), an assistant professor of dermatology and founder of the U-M Cancer Center's Multidisciplinary Merkel Cell Carcinoma Program. The U-M Health System is one of just three medical centers in the country with a treatment and research program devoted to Merkel cell cancer. "It's so rare that no one sees enough patients to develop expertise in how to treat it. Many physicians see just one or two patients with Merkel cell cancer in their entire careers."

Because the disease is so rare and no one specialty treats patients with this type of skin cancer, treatment is inconsistent. Head and neck surgeons have one protocol; surgical oncologists have another. It is often misdiagnosed as basal-cell cancer and long delays before diagnosis are common as patients are passed from physician to physician.

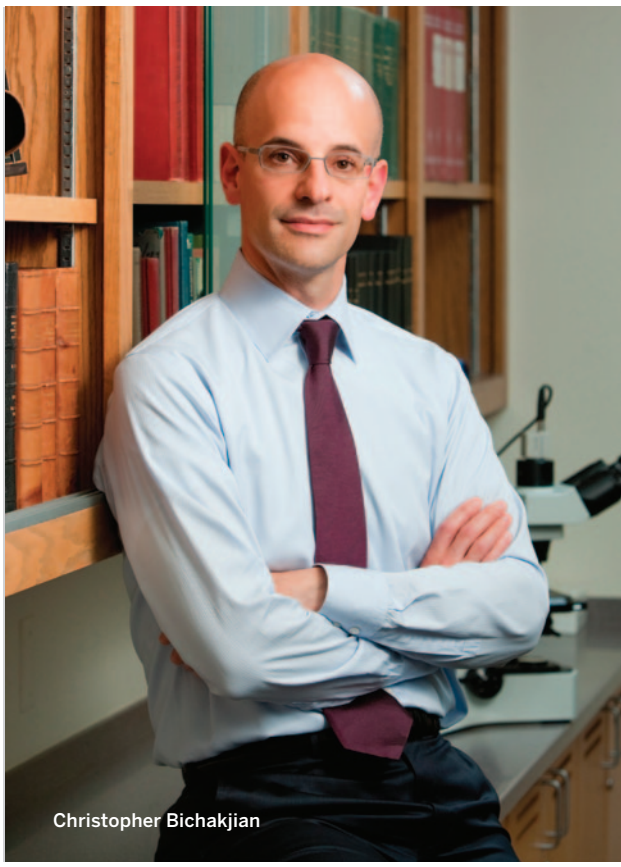
"Another difficulty with Merkel cell cancer is that it doesn't look like anything in particular," says Bichakjian. "It has no characteristic features, so the patient thinks it's just a little red bump and it's not growing or hurting. When they eventually see a physician, the doctor says it looks like a little cyst or basal-cell cancer. Eventually, it gets biopsied, but there's often a delay. That's a problem, because Merkel cell carcinoma is an aggressive disease that spreads from skin to lymph nodes. If you can catch it in a lymph node before it goes anywhere else, you have a chance of containing it."

Merkel cells in skin are connected to peripheral nerves that transmit touch, temperature and pain signals to the brain. Researchers don't understand exactly how Merkel cells work or what causes them to become malignant, but they know the cancer is most common in elderly people or those without a healthy immune system. One intriguing clue was the discovery in 2008 that genes from many Merkel cell carcinomas contained DNA from a type of virus known to cause tumors in mice. This led some researchers to speculate that Merkel cell cancers could be caused by infection with the virus.

"You find the virus in about 80 percent of Merkel cell tumors," says Bichakjian. "But whether the cancer is caused by the virus is not yet proven. We know that 60 percent to 70 percent of the population has been exposed to this virus and the vast majority of these people are not going to get Merkel cell cancer. Plus, 20 percent of tumors don't have the virus at all."

Early in 2006, Bichakjian established the Merkel Cell Program, which is modeled after the Health System's 20-year-old Multidisciplinary Melanoma Program. In the last four years, the program has treated 160 patients from Michigan and surrounding Midwest states and Bichakjian gets weekly calls from patients or family members in other areas.

"When we started the program, one of our first goals was to develop a treatment algorithm based on our experience and the literature that's out there," says Bichakjian. "We don't have a miracle drug for Merkel cells. Our scalpels are no different from other surgeons'. But what we can offer is a multidisciplinary, consistent approach to treatment with detailed data on how our patients respond. After four years, we feel comfortable that we own Merkel cell and its management." —SP



Christopher Bichakjian

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