Finding links to cancer

Masonic Cancer Center researchers work to identify carcinogens in the world around us—as well as ways to avoid them

When scientists talk about “environmental” causes of cancer, they don’t mean that carcinogens lurk in every tree and stream. They’re referring to anything that enters or interacts with the human body—sunshine, food, water, alcohol, radiation, cigarette smoke—and examining them for their potential to cause renegade cell growth. And as they now know, environmental factors are linked to as many as two out of every three cancers diagnosed.

DeAnn Lazovich, Ph.D., M.P.H., is one of many Masonic Cancer Center, University of Minnesota scientists investigating environmental factors with causal links to cancer. Lazovich has focused on the relationship between indoor tanning and melanoma, an often deadly form of skin cancer.

“What we discovered,” says Lazovich, “is that there is a definitive link between indoor tanning and melanoma. The more one tans, the higher the risk of getting melanoma.”

But what, if anything, can scientists do to stop people from engaging in risky behavior once a link to cancer has been identified? Like so many of her colleagues, Lazovich is every bit as interested in how to use research findings to craft public policy as she is in the research itself.

“In Minnesota, children under age 16 must have written permission from a parent, delivered in person, before they can use indoor tanning facilities,” explains Lazovich.

continued on page 2
Lazovich. “But we found that many parents aren’t aware of the law and that many tanning businesses don’t enforce it.”

Lazovich is now working closely with the Minnesota Cancer Alliance to pass legislation that would ban indoor tanning in Minnesota for anyone under age 18, a safety measure she believes is especially necessary because girls start indoor tanning around age 16.

“We’re now seeing melanoma in people in their 20s and 30s,” says Lazovich. “It’s one of the fastest-growing preventable cancers. By hook or by crook we need to get this information out so we can stop people from exposing themselves to risk unnecessarily.”

The most infamous cause

Perhaps the best-known of all environmental causes of cancer is the cigarette, which contains numerous carcinogens and produces smoke that includes many more (see below).

The news got even worse in January when the Surgeon General issued a report on the 50th anniversary of the 1964 landmark report on smoking and health. New findings have now linked smoking to such health consequences as macular degeneration, ectopic pregnancy, and rheumatoid arthritis.

Masonic Cancer Center researcher Dorothy Hatsukami, Ph.D., who holds the Forster Family Chair in Cancer Prevention, has been at the forefront of tobacco research since the 1980s, when the University became a leader in systematically examining and confirming a physical dependency on tobacco products.

Decades later, working with colleagues including Stephen Hecht, Ph.D., who holds the Wallin Chair in Cancer Prevention and Genetics, Hatsukami conducted studies proving the harms of secondhand smoke, providing support for the Minnesota Legislature’s decision in 2007 to implement a statewide smoking ban.

America’s love/hate relationship with cigarettes began when the first Camels rolled off the packaging line in 1913. But 100 years later, the scales have tipped heavily toward “hate.” Thanks to six decades of research, we now know that the Marlboro Man was just a guy who would have been three times more likely to die because he smoked.

The Masonic Cancer Center has been at the forefront of much of that research, leading the way on early investigations that confirmed that cigarette smoking is physically addictive; University of Minnesota scientists also played key roles in identifying individual carcinogens in tobacco.

Here’s what we know about cigarettes now that we didn’t know 100 years ago:

- Cigarettes have more than 30 known carcinogens, including arsenic, benzene, and cadmium.
- Cigarette smoke contains more than 4,800 chemicals, 69 of which are known to cause cancer.
- According to the Centers for Disease Control and Prevention (CDC), cigarette smoking now accounts for one in five deaths in the United States.
- The CDC has also pronounced tobacco use the No. 1 preventable cause of death in the country.

Do electronic cigarettes, or e-cigarettes, offer a safe alternative? Masonic Cancer Center researchers, concerned about the lack of scientific information on the new battery-powered cigarette simulators, recently launched an investigation to find out. Stay tuned.
Today Hatsukami is concentrating on developing the scientific basis for policies that might reduce tobacco-caused death and disease, such as reducing the addictiveness and toxicity of tobacco products.

**Beware charred meat**

Masonic Cancer Center member Robert Turesky, Ph.D., is considered a world expert in heterocyclic amines (HCAs)—chemicals formed when meat is cooked at high temperatures.

Turesky has long been investigating how the human body transforms that class of chemicals, which are carcinogens, into DNA-damaging agents. He has fried, broiled, grilled, and charred meat to discover what temperature creates the chemicals. He has measured HCAs to determine what amount causes DNA damage. He has tested human hair follicles, where the chemicals get trapped, finding the carcinogen in the hair of meat-eaters but not in vegetarians.

“We now know the answers to a lot of the questions about exposures to HCAs,” he says, ‘and the short answer is, ‘Don’t eat charred meat.’ But remember, if this carcinogen is in your body, it doesn’t necessarily mean you’re going to get cancer. It just means you’ve consumed cooked meat with this carcinogen.”

**A mystery, contained in wax**

Turesky’s most recent discovery, published in *Chemical & Engineering News* and presented to the American Chemical Society, provides a way for toxicologists to go back through wax-preserved tissue samples from people diagnosed with cancer and find clues about the origin of the cancers with a suspected environmental cause, he says.

More than a billion of these preserved tissue samples are thought to be in storage around the world. But scientists have been stymied because, despite years of trying, the mystery contained in those samples—preserved in a formalin solution, then embedded in a block of paraffin wax—has been tough to crack.

Turesky, who has also been studying a carcinogen called aristolochic acid that is found in certain traditional Chinese herbal medicines, used a technique called mass spectrometry to measure and identify the carcinogen linked to DNA in a fresh, frozen tissue sample. That was significant in itself. But to get a handle on how widespread the exposure to aristolochic acid is worldwide, he needed to examine older tissue samples—the ones preserved in formalin.

It’s his success in unlocking the mysteries of those samples using the same technique that has the American Chemical Society so excited.

“With this new ability to identify and measure carcinogen DNA adducts in preserved tissue samples,” says Turesky, “we can see exactly which chemicals coming from environmental exposures are doing the damage.”

*To learn more or make a gift to this research, contact Cathy Spicola at 612-625-5192 or cspicola@umn.edu.*
Jill Siegfried, M.D., explains how Masonic Cancer Center scientists are working to speed up research projects showing the most potential.

What happens once a scientist discovers something he or she believes could be useful in the fight against cancer?

JS: Let’s say the investigator discovers a protein that helps make a cancer grow faster; we’ll call it X. So the goal is now to find ways to inhibit X from “feeding” the cancer. Researchers might then identify a molecule that, in a petri dish, prevents X from growing. At any time along the way, things can and do fall apart, which means you start again.

At what point does the new compound get to human trials?

JS: Scientists need to be sure it won’t cause more harm than good. Is it too toxic for humans? Or is it metabolized so quickly that it doesn’t even get to X? They’ll test these things in other mammalian species first, before finally bringing it to human clinical trials.

Is there any way to speed up the process?

JS: That’s the purpose of the Masonic Cancer Center’s Cancer Experimental Therapeutics Initiative. It focuses on identifying the most promising therapies across all the labs and making sure that limited funds are channeled in the most effective way.

Would more money help get drugs to market faster?

JS: Absolutely. Economics come into play at every stage: in the lab when you’re applying for grants to get the work going, finding partners to help finance clinical trials, pharmaceutical companies deciding which drugs will make the most money … We’ve had a tremendous shutdown of government funds for research, so private philanthropy and business partnerships have become critical. It’s heartbreaking to see so much promising research limp along because investigators don’t have funds to keep going. But what people should realize is that the No. 1 thing that drives new discoveries is the unwavering commitment of the scientist to make it happen.
Brad Hoyt fell in love with racing as a boy when his father took him to see the movie “Grand Prix.” So when he found himself the winner at the finish line of the premier Grand Prix of Monaco in 2008—in a 1969 Formula One Ferrari similar to the one in the movie—he had to pinch himself.

“I called my dad from Monaco,” says Hoyt. “I said, ‘Here I am, 55 years old and a roofer from Richfield. And I’m racing in Monaco. … It doesn’t get any better than this.’”

After returning home to Minnesota, all Hoyt wanted to do was get back to Monaco and win again. But a diagnosis of myelodysplastic syndrome (MDS) in April 2011 threatened that plan—and his life.

Hoyt was quick to seek treatment for his MDS, a type of cancer in which the bone marrow doesn’t make enough healthy blood cells. He promptly flew to Seattle to be seen by the doctors he believed were “the best in the country.” To Hoyt’s surprise, those physicians suggested he return home and be treated by Erica Warlick, M.D., a hematologist/oncologist with the Masonic Cancer Center, University of Minnesota.

“I remember she said to me at our very first meeting, ‘We’ve got to cure you. Those children need a father,’” recalls Hoyt, a father of four. “I knew that she was going to take care of me like I was her own dad.”

Warlick and the rest of Hoyt’s care team took quick action, too. He started treatments 10 days after his diagnosis, and on July 19, 2011, he underwent the blood and marrow transplant at the University of Minnesota Medical Center, Fairview that he credits with saving his life.

Hoyt recognizes that many years of research are behind the transplant he received and that much of that work happened at the University.

As a way of showing his gratitude, in 2012 Hoyt made a gift commitment to create the Hoyt Fund for MDS Research, supporting the work of Warlick and Masonic Cancer Center colleague Julie Ross, Ph.D. Today Ross is leading the world’s most comprehensive study of MDS. The team aims to uncover the causes of MDS as well as find better ways of diagnosing, managing, and treating it.

It’s the combination of investigators—lab scientists, clinicians, and epidemiologists—that makes the Masonic Cancer Center’s research stand out, Warlick says.

“All of these components working together help us to better understand the disease biology and then help better understand how to develop therapies so we can treat the patient,” she says. “And that’s the most important thing—treating the patient.”

This sensibility was clearly evident to Hoyt throughout his treatment and recovery. He says that Warlick’s and Ross’ determination inspired his support. “They’re just really emotionally and personally invested in finding a cure,” he says. “I know I wouldn’t be here if it wasn’t for the research and the dedication these people have.”

He wouldn’t have been able to return to Monaco in 2012 and win again, either.
At 78, volunteer Hinda Litman now has a shock of snow-white hair but retains the same joyful energy she brought to University of Minnesota hospitals more than 35 years ago, when she first volunteered as a patient visitor. Since then, she’s worked in the surgery lounge, with hospice patients, and now in the Masonic Cancer Clinic—wherever there has been a patient in need, Litman has shown up.

Mary Sumpmann, M.S., R.N., the Masonic Cancer Center’s associate director for administration, describes Litman as “a tenacious bulldog” when it comes to making sure patients get what they need, whether it be a little extra TLC, help navigating the hospital system, or a quick snack.

“Hinda’s the one who people go to if they need a shoulder or an ear,” says Sumpmann, “because she always takes the time to get to know the patients and their families. It’s not her job to be here; she does it because she’s passionate about it.”

What most patients don’t realize is just how far Litman will go to help the people who cross her path. For one young woman who had lost a leg to osteogenic sarcoma, Litman arranged a trip to Disney World, personally supplying spending money and airfare. She has organized similar trips for other patients over the years, never hesitating to dip into her own pockets to make it happen.

Once, when she realized the mother of an out-of-state patient couldn’t afford a hotel room in Minneapolis, Litman brought her home, where the woman ended up staying for more than a month.

“Everyone should be so fortunate to have a volunteer like Hinda,” says Jean Jacoby, executive assistant for administration at the Masonic Cancer Center.

So what has driven Litman to spend more than 22,000 hours of her life volunteering at the University?

“My father got cancer when I was young and had to go to New York for treatment,” she recalls. “My brother went with him, and there were so many people there who helped them. I remember thinking, ‘That’s what I want to do one day,’ because I could never forget how those strangers helped our family.”

So every Monday, Litman heads to campus to help with the lung transplant support group. Then she comes back on Wednesdays and Thursdays to staff the information desk at the Masonic Cancer Clinic, sometimes putting in 10-hour days to make sure everyone gets taken care of.

“I always think on the way home how lucky I am,” she says. “I see so many people who aren’t doing as well. I tell my grandkids, ‘Don’t complain! Every day is a gift!’ And if the house has a few cobwebs because I’m at the hospital, well, so be it. You have to have perspective about what’s important.”

Make a gift to honor someone who has made a difference in your life at give.umn.edu/cancer.
This story is short. Not much is known about metastasis. And that’s the point.

“Patients don’t die from primary tumors,” says researcher Akhouri Sinha, Ph.D., of the Masonic Cancer Center, University of Minnesota. “It’s the metastases that kill them.”

Metastasis—the spread of cancer from its origin—is responsible for about 90 percent of deaths from human solid-organ cancer, he says. Many metastasizing cells go to lymph nodes, where cells of the immune system are supposed to seek out and destroy them. Although some metastasizing cells escape to the bloodstream or bones, lymph nodes are so important that the extent to which metastasizing cells have invaded them is used in staging cancers.

After cancer surgery, pathologists examine lymph nodes from near the original tumor. Usually, they report only whether nodes are positive or negative for cancer cells.

But there has to be more to the story, because some patients with positive nodes survive a long time, while others die within a few years.

In a recent study, published in Anticancer Research, Sinha and three colleagues looked deeper into what happens in nodes after cancer cells have metastasized there, seeking to explain the difference in survival times. They found that in some nodes and in some patients, the immune system seemed to be doing its job because the scientists saw dead and dying cancer cells in the nodes. In others, however, the cancer cells seem to have the upper hand; they weren’t dying.

In other words, they saw two kinds of metastatic tumor cells: those that were at least partially vulnerable to the immune system, and those that were not.

The researchers believe that patients whose nodes show significant cancer cell death will do better than those whose nodes show little or none because that may signal the rise of cells resistant to attack by the immune system. These patients may require more aggressive therapy.

Sinha suggests that people who have cancer-positive nodes ask to have their pathologist test to see whether the immune system or the cancer cells appear to be winning the battle in the nodes. (The test is routine in pathology labs.) Armed with that knowledge, their physician may want to adjust their therapy.

“Our study provides a basis for pathologists to assess the course and fate of metastatic cancer cells in nodes, which may help predict outcomes for patients,” says Sinha, who also is a professor of urology and genetics, cell biology, and development at the University. “This approach can be applied to breast, lung, pancreas, colon, and other solid-organ cancers.”

The researchers are now looking into the survival times of the patients whose lymph nodes they examined to see how survival correlates with the degree of cancer cell death in the nodes. They will also compare the genetic composition of metastatic cells in lymph nodes to those of cancer cells in the primary tumors to learn whether a cell’s genetic makeup determines where, and whether, it will metastasize.
Since scientists now know that between 5 and 10 percent of all cancers are caused by abnormal genes inherited from a parent—often called hereditary cancers—Masonic Cancer Center researchers and clinicians are increasingly focused on making sure that patients understand their family history to minimize their cancer risk.

The William C. Bernstein, M.D., Familial Cancer Registry has played a key role in that effort. Opened in 2008 with a philanthropic gift, the registry initially screened cancer patients for hereditary risk using a simple questionnaire. Follow-up research has focused on family members’ willingness to pursue genetic counseling, an important part of cancer control in families at an increased risk.

Armed with information from the Bernstein Registry’s studies, the University of Minnesota team is now implementing a system that will soon allow patients to input their family histories electronically. As doctors spot red flags—multiple family members with the same or related cancers, early cancer onset, multiple primary cancers, or unusual cancers, for instance—they can urge patients to seek genetic counseling.

“Individuals with strong family histories of cancer too often believe that there is nothing they can do to reduce their risk,” says Robert Madoff, M.D., medical director of the Bernstein Registry. “In fact, the opposite is true. ... For those who do carry harmful gene mutations, cancer risk can be very substantially reduced with increased screening and sometimes with prophylactic surgery.”

To make an appointment with a cancer genetics counselor, call the Masonic Cancer Clinic at 612-625-5111.