Is Cancer Inevitable?

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Is Cancer Inevitable?
OUR BODIES ARE GENETICALLY PROGRAMMED to work with all the parts collaborating. In many ways, it reminds me of the thousands of doctors working worldwide to solve the riddle of cancer. When things are functioning, everything inside us comes together, pulling in the same direction. Our normal cells are equipped with regulatory mechanisms that in many cases “can correct damage, abort the process, or even cause hopelessly wrecked cells to destroy themselves,” as Mark Wolverton wrote in Wired.¹

Yet, as we all know and as we’ve seen in our lab, the system becomes more prone to fail us as we grow older. Somewhere a vital protein is being altered or destroyed, and that mutated cell divides to create another; as the process outpaces the growth of normal cells, this disease becomes a dangerous reality for another person. As we grow older, internal natural selection will begin to favor the cancer mutations, and then they may break away and metastasize elsewhere in the body.

At first glance, cancer appears to move in lockstep with
aging. The chances of our getting it, in some form, rise as life expectancies go up around the world. We all know people who’ve combatted it until they couldn’t fight anymore. Still, when we begin to look beyond the raw numbers and textbook definitions for cancer, we can glimpse a different world with more optimistic and hopeful outcomes. We may never cure cancer, at least not all of its many types. Still, it’s clear that we’re doing a better job of understanding this disease and moving toward ever new ways to keep it at bay and battle it successfully when it crosses the threshold.

Things aren’t always as they appear to be. We’ve heard that a million times in our lifetimes, and it even holds true with how cancer cells appear under the microscope in the lab. Take a look at a normal monocyte cell. With its long, treelike dendritic branches, it’s likely one of the creepiest things you’ve ever seen. But these monocytes help the body fight infections and viruses. They are a basic component of any vibrant immune system.

A melanoma cell, on the other hand? While melanoma cells are dangerous and invasive, they don’t appear to be anything special at first glance. They’re mostly round, maybe a bit oblong at times. Seemingly nothing to worry about, right? Yet they represent a rule of cancer research: Appearances can be deceiving.

If things aren’t necessarily as they appear that can be a cause for hope, too, especially if we’re able to change or alter a few key variables. Elsewhere in the body, other cells serve
as sentry guards or traffic cops. These are dendritic cells, and they can alert T cells, the body’s so-called foot soldiers, to attack the tumors. Yet, as we age, these sentries and soldiers can weaken, and now the tumor cells are better able to do their work unchecked.

Identifying and helping key cells and systems is one way forward in terms of therapy. We recently published a paper that details how blood vessels growing in normal cells are dictated by a specific protein. As we age, we lose that protein and another protein takes over. Until recently, the cancer drugs we had developed only targeted the first protein, which did older patients little or no good at all. Now we’re focusing on the role of that second protein. Such instances emphasize why we need to be specific about age and what age groups people fall into. In the case I just mentioned, if you’re under 45, the drug works, at least to some extent. But if you’re over 45 it doesn’t, because the very protein that you’re trying to target doesn’t exist in the body anymore. We’re doing more studies with the emphasis on older patients. Such research has been largely overlooked in the past; that’s no longer the case in labs like ours.

Also, we need to keep in mind that cancer treatment and care can differ greatly from what we’ve found in other chronic diseases, such as heart disease or diabetes, where patients can be given bypass surgery, stents, or statins. Surgeons fix heart valves mechanically. If the operation is successful, it’s done and the patient moves on with their life. That’s not usually the
case with many forms of cancer, although sometimes a tumor can be surgically removed before it metastasizes, and chemotherapy or other treatments can give that patient many additional years with their families.

Our understanding of cancer is changing quickly, and with it our ability to manage and even control the disease. And that’s being borne out across many forms it may take—whether breast cancer, lung cancer, melanoma, or other types. The odds of our being able to manage it continue to increase. That’s where the advances in immunotherapy are so promising. We need to remember that often only a few cells and how they react and respond to therapy can make all the difference. If we can gain a bit more insight and understanding about these pivotal cells, we’ll be even more able to successfully target them for treatment.

Our immune system is divided into two categories. The dendritic cells, the traffic cops, belong to the innate immune division. Others here include the mast cells, which produce histamines to attack allergens, the neutrophils, which kill bacteria, forming pus, and last, but certainly not least, we have the macrophages, with long tendrils to better snag their targets. This type of white blood cell is named after the Greek words for “big eaters.”

The innate system needs to work in concert with the adaptive system, which includes B cells and T cells. Both of these are formed in the bone marrow and work hard to keep the cancer cells in check. How well one’s immune system works
is determined largely by heredity. It comes down to the cells you were born with, whether you had a mother who had breast cancer, for example, or another relative with a different form of cancer. In such cases, cancer borders upon an inevitable diagnoses because of the major role genetics can play—but mortality is not necessarily inevitable. The advances in breast cancer detection and treatment are a perfect example of this, with many more women surviving for years and even decades after their diagnoses.

Cancers that are behaviorally driven are clearly not inevitable. If you smoke, we know that can lead to lung cancer. If you’re prone to spend a lot of time in the sun, that can lead to skin cancer. With these and other forms that are avoidable, including those connected to obesity, it’s about education, getting the word out; when that happens, the diagnosis and death factors can be lowered exponentially.

Also, we need to further embrace the power of early detection—and make it accessible (financially and geographically) to more people. Screening procedures, some of which were put in place decades ago, have proved to be effective in reducing the worst impacts of cancer by catching it in earlier stages. This applies to genetically, behaviorally, and even some environmentally driven cancers.

Thankfully, the science is improving every day. New trials are held, new research studies are published, new drugs are approved. So, if we don’t want cancer to be inevitable, we need to stay educated on the latest advances, and understand how it
affects myriad populations in unique ways—young, old, male, female, Black, Hispanic, Asian, white. That goes for everyone in the health care community—from the doctors to the patients.

What makes cancer different from other chronic diseases is that if a few cancer cells escape detection or treatment, the disease will likely return. That’s been a given for a long time, and some may find this frightening. To me, though, it’s one of the most intriguing things about cancer—what makes it such a puzzle. For example, studies indicate that if tumors leave the primary site early in their life, they can travel to the distant sites, and they may then just sit there, dormant and in wait. As we age different changes can drive these tumors out of dormancy—can make them grow and present with metastasis. If we can better understand how and why these cancer cells are moving about, talking with other cells, the role that age can play, cancer becomes less inevitable. With our research, we’re defining the factors that are in play and beginning to determine how everything fits together.

CONSIDERATIONS TO KEEP IN MIND

Don’t sunbathe.
Don’t smoke.
Don’t eat bad stuff.
Exercise.
Those are my basic guidelines for dealing with what I call environmental “insults”—the behavioral side of cancer prevention. At first, this may sound like the do’s and don’ts that your mother once told you—something like wearing your coat when it’s cold or slipping on your galoshes when it rains. I want to emphasize that I’m not scolding or shaking a finger at anyone here. That said, if we can each take more responsibility for our basic health, it can greatly help our efforts against cancer.

People may not realize that when they smoke or lie in the sun at the beach (or work outside for a living), they’re damaging normal cells and driving their transformation to cancer cells at that particular moment. Indeed, these insults drive a chronic accumulation of genetic damage that builds up over time. When this is linked with the immune system’s increasing inefficiency as we age, it opens the door to any number of problems. Over time, the microenvironment can become “the ideal soil for the abnormal cancer seed,” wrote Azra Raza, author of The First Cell.

We’re finding that some of this genetic damage has been incurred early on, before the age of 20. The cells are accumulating mutations and it’s not just the cells that ultimately become melanoma cells. It’s also the normal cells that surround those melanoma cells, and the breakdown of these normal cells can grow over time. Some cells may be genetically reprogrammed to become a melanoma tumor and can grow and metastasize.

Obviously, we know that the body changes as we grow
older. We begin to have gray hair or we may have a bit more trouble moving around. Such factors can serve as a reminder that we need to monitor things—really look out for ourselves on a number of levels. The American Cancer Society recommends that men and women, ages 50 years and older, meet with their health care providers and be regularly tested: men for colon, prostate, and lung cancer; women for breast, cervical, colon, and lung cancer.

In the lab, we’re reminded that one’s lifestyle can be so important, too. Obesity is emerging as a risk factor with multiple types of cancer (including liver, thyroid, breast, ovarian, pancreatic, stomach, colon, and kidney cancers), and, again, age is a key factor, perhaps in an unexpected way. A 2019 study funded jointly by the American Cancer Society and the National Cancer Institute found that six of 12 obesity-related cancers increased in successive generations of adults ages 25 to 49. Lack of physical activity and greater consumption of calorie-dense fast foods were cited in the study. “Due to the obesity epidemic over the past 40 years, younger generations worldwide are experiencing an earlier and longer-lasting exposure to excess adiposity over their lifetime than previous generations,” the researchers wrote. It’s thought this may be linked to the alarming increase in the rates of colon cancer in younger patients.

I was recently talking with a colleague who’s studying how increasing one’s fiber intake, adding a few more vegetables
and whole grains to the daily diet, can make a world of difference, too. She’s finding these small measures to be important in the treatments she’s doing for melanoma. After upping their fiber intake, her patients were seeing better test results and response to therapy within a few weeks.\(^7\)

It’s best to avoid fast foods, highly processed meats, and sugary drinks as much as possible. Those fall into my category of “bad stuff.” In comparison, whole grains, citrus fruits, and vegetables (carrots, garlic, and onions) have proved to be effective cancer-fighting foods. Longitudinal studies have also indicated that people who exclude meat completely from their diet have far fewer cancer diagnoses.\(^8\) Vegans in these studies had the lowest rates of cancer. It isn’t only the direct plant-based food benefits (including higher levels of fiber) driving the findings, though; vegans and vegetarians are also less likely to be overweight, which further reduces their risks.

The link between tanning and cancer, of course, is much better established. With that in mind, I’d urge everyone to use sunscreen (a sun protection factor [SPF] of 30 or above) and wear a wide-brimmed hat when they’re outside. Most skin cancers are caused by too much exposure to ultraviolet rays. Their strength depends upon several factors, including time of day (they’re at their strongest during mid-day), time of year (stronger in the spring and summer), and altitude (stronger at higher elevations). Also, keep in mind that UV rays are present even on cloudy days. A sunscreen that has an SPF of 15 can
filter out about 93 percent of ultraviolet rays, according to the American Cancer Society. In comparison, a SPF sunscreen of 30 eliminates nearly 97 percent. Still, remember that no sunscreen offers complete protection, and none are waterproof.

In our lab, we’re investigating the effect UV rays can have as we age. Asurayya Worrede, who came with me to Johns Hopkins from Wistar in Philadelphia, is directing a new study in which we’re analyzing the differences as well as the similarities between UV-induced proteins and skin cells. We take cells from punch biopsies of the skin, usually in the upper arm because that hasn’t been as exposed to the sun over time as much as the face and other areas of the body. We have several dozen people in various groups—men and women, ages 25 to 35, and men and women, ages 55 to 65.

In the lab, we have a machine that appears to be nothing more than a black box. Yet with this machine, a UV irradiator, we can control the dosage level, as well as the type of the UV rays to which we expose our experimental cells. UV rays are divided into three major categories— UVA, UVB, and UVC. For this study, such differences aren’t a major factor. Thankfully, we don’t have to worry about UVC rays in our everyday lives as the ozone layer shields us from most of their impact. It’s UVA and UVB that age and wrinkle skin cells, and they can damage the cells’ DNA, too. Of the two, UVB has slightly more energy.

In another study, we’ve been varying the doses of UV as we explore how these rays can impact younger patients. For
example, does such damage build up over time? And if so, how does that occur? In addition, we’re radiating samples of skin of older people. Can such cells, even after years of exposure, take a turn for the worse? “The great thing about our lab is the range of questions being asked,” Asurayya says. “They can be in-depth and far-reaching. There’s really no limit at all.”

When it comes to smoking, no form of tobacco is deemed safe today. Also, it’s important to avoid second-hand smoke as much as you can, as that can lead to several forms of cancer. A recent study by the American Heart Association discovered that people who quit smoking cigarettes before age 40 lessen their chances of premature death from cardiovascular disease by 90 percent. The study tracked nearly 400,000 people for 17 years and found that smokers were three times more likely than nonsmokers to die of heart disease or stroke.

In recent years, our understanding of exercise, how important it is, has grown, too. The American Cancer Society recommends that most adults should strive for 150 minutes to 300 minutes of moderate physical activity a week. It can be difficult to begin a new exercise plan on your own, so partner up with a friend. Catch up with each other during a brisk walk. With moderate exercise, you should be able to talk while doing so. After you’ve gotten started, you can increase the heart rate in future weeks and months.

Yes, we’ve probably heard much of this advice before. Still, the new studies and the work in our lab and from other places
Protecting Yourself 
and Your Family

Each of us can help better our odds by being more vigilant about our health. Annual checkups and screenings could save you or your loved one’s life, and they should be part of your health care plan. Early detection is one of the most vital tools in the fight against cancer, as self-examinations and scans help technicians and doctors reveal telltale indicators in time to fight them successfully with surgeries and treatments. But, many don't go for these screenings, even though many health insurance plans cover these tests and visits completely as part of their wellness efforts. A survey in 2020 by Consumer Reports found that 52 percent of Americans say they never go to the doctor to have their skin checked. Reversing that trend alone would improve melanoma survival rates and save thousands of lives each year.

For skin, breast, cervical, prostate, lung, and colon cancers, annual screenings are recommended by the age of 50. At such appointments, be sure to discuss your family's medical history, asking relatives beforehand if necessary. While some cancers are harder to detect, pay attention to your body through self-examinations as well as noting symptoms that seem out of the ordinary. Jot down any symptoms or discoveries you've made regarding spots, lumps, coughs, pains, or other potentially problematic physical signs before your visit; having a written list will help you remember to tell your doctor each unusual thing you've noticed.

If you have a family history of cancers like melanoma (grandparents, parents, siblings), have recently had cancer yourself, or have more than fifty moles over your body, you may need to see a dermatologist or other specialist more frequently than every 12 months. There's peace of mind
in being checked head to toe by a dermatologist using a dermatoscope, with its magnifying lens and pinpoint lighting, and by technicians using the latest equipment and software during mammograms, biomarker lung cancer screenings, and colonoscopies. Researchers and inventors are also focused on new methods that can reveal cancer in early stages, including a blood test that detects more than fifty forms of cancer with 99.3 percent specificity, some before symptoms appear, based on a recent trial with nearly 7,000 participants.

Even if you’ve been a sunbather, smoker, or have other habits or genetics that could lead to cancer, it need not be a certainty that you will get it or succumb to it if it’s diagnosed. Begin conversations with your family doctor now to explore how you can work together to put the brakes on detectable cancers.

Notes
are a steady reminder about how important such daily measures can be. Take care of yourself. When we all follow the science (in addition to using our common sense), it makes cancer less inevitable.

**ADVANCES IN IMMUNOTHERAPY**

Immunotherapy or immune-cell therapy uses the body’s immune system to move against cancer. This approach describes a wide range of treatments, and it holds so much promise, especially with melanoma, because it targets specific mutations in a person’s cancer. Steven Rosenberg, chief of surgery at the National Cancer Institute, told the *Wall Street Journal* that immunotherapy is the new “blueprint” in therapy.¹¹

While immunotherapy is not used as widely as chemotherapy, surgery, or radiation therapy as of yet, it’s on the rise (sometimes in combination with those other therapies), and it’s one of the most widely used forms of therapy in treating melanoma. In the last few years, we’ve seen a number of advances within immunotherapy, including T-cell transfer therapy, monoclonal antibodies, immune system modulators, and immune checkpoint inhibitors. Jim Allison is widely recognized for having discovered immune checkpoints and applied them to cancer therapy,¹² and for this he won the Nobel Prize in 2018 along with Tasuku Honjo. Checkpoints are mechanisms by which immune cells are regulated, such that when an immune response is mounted, it doesn’t flare out of control and attack
cells in the body indiscriminately. However, cancer cells co-opt these mechanisms, and use checkpoints to inhibit the immune response to the tumor cell, such that the tumor can escape from attack and clearance by immune cells. Blocking checkpoint proteins, therefore, is proving to be especially effective in treating melanoma, and we achieve this by using antibodies against immune checkpoint proteins, to essentially bind them up and stop them from triggering an initiation of a checkpoint. These new drugs release the natural brakes on the immune system, allowing them to really go after the cancer. By blocking checkpoints, we can free the T cells and other immune system foot soldiers to move against the cancer.

Some newer advances in understanding the way the immune system works in cancer include the discovery of a T-cell co-stimulatory signal. This is nicknamed “the gas pedal,” as it can heighten the T-cell activity. It’s one thing to release the brakes within the immune system, to allow the T cells to attack the cancer. It’s quite another to accelerate the process, to make it more effective by speeding things up. This gas pedal/brake analogy has long been used to describe oncogene activation in cancer—an oncogene is a mutated form of a gene (known as the wild type) that drives abnormal cell growth. This can lead to the growth of cancer cells. Mutations in genes that become oncogenes can be inherited or caused by being exposed to substances, those behavioral insults, in the environment.13

What’s wild is that so much else can also impact the immune microenvironment and response to therapy. We see
that older patients actually do much better on immune checkpoint therapy. Why? It could be the high mutational burden in these tumors, or the differences in immunomodulatory signals. My friend Jen Wargo at MD Anderson is showing that the microbiome of the gut can also affect patient response to immunotherapy, further feeding the hypothesis that diet and exercise can help provide a better outcome. Already we’re seeing such insights and changes in therapy extend to the patients. It used to be that you had to go in for an IV procedure for such treatments to be effective. It was done as an outpatient, going to the hospital, doing the entire procedure there. Increasingly, patients are able to do much of their treatment at home, in pill or capsule form, and are even being provided with “meals to go” in clinical trials to manipulate microbiota. Also, we’re becoming better able to monitor progress by various types of scans and blood work. Such tests can measure the size of the tumor and any changes in the blood work.

As a result of such new procedures, we’re seeing a growing group of cancer patients who are living longer. Not that long ago, Stage IV melanoma was typically fatal within a year. Today, we’re seeing more of these patients live years longer, some even eventually being declared cancer-free. A famous example is former president Jimmy Carter, who was diagnosed with melanoma that eventually spread to the brain. He was treated with checkpoint inhibitors, and several years later, continues to thrive, building houses for Habitat for Humanity,
and generally benefiting society through his kind and generous actions, and the work of The Carter Center.

By using the power of the immune system, we’re transforming this field of medical care. Today, roughly half of the people diagnosed with advanced melanoma have become so-called super survivors. One of them is my friend T. J. Sharpe. A Stage IV melanoma patient, T. J. was diagnosed in August 2012 with melanoma tumors in multiple organs, only weeks after his second child was born. Since then, he has undergone six surgeries and four immunotherapy treatments and has been involved in two landmark clinical trials. He’s chronicled his journey on a blog and in a YouTube video:

When I was 37, I went into the ER with what I thought was a spiking fever and left 16 days later with a Stage IV melanoma diagnosis. The oncologist who admitted me gave me my tumor report. And when my wife Jen asked him what we were looking at, he said, “I’ll be surprised if he’s here in two years.”

So, after I was diagnosed, I had a lot of time for research, sitting in the hospital for two weeks, to determine what my next steps were. I knew that it wasn’t going to be just a regular standard of care, I had a two-month-old son. I didn’t want him to grow up without a father, and I was determined to find the best treatment.

It was discouraging realizing I had so few options,
until I started understanding the clinical trials that had different drugs that weren’t available to the general public. After realizing that clinical trials were likely my best option, we began looking at every available trial for a Stage IV melanoma patient.

We decided to get several second opinions and found a cancer center that offered a unique trial, and one that I became the first patient ever to get a series of therapies in a certain order. That to me was going to give me the best chance to watch my children grow up.15

T. J. empowered himself. He studied what he was up against, networked like crazy, and enrolled in a suitable clinical trial. Incredibly, he ended up receiving much of his treatment only a short drive from his home in Florida. He’s not only an example of how proactive a patient sometimes needs to be, but, more importantly, he’s an example of the promise that these new rounds of treatment for melanoma may hold for a growing number of people.

**LOOKING TO THE FUTURE**

We’ve refined drug treatments so that patients are living five to ten years longer. With nearly a quarter of those patients, specifically those with melanoma, we’re using the word “cure.” Things are moving at breakneck speed, which gives those of us
in cancer research confidence and reason for optimism. And it’s not just in melanoma research. The work with breast cancer is advancing rapidly, and in colon cancer, too. Even in pancreatic cancer, advances are being made.

We’ve also begun to witness that the work being done in one field, say melanoma, can be extrapolated to other forms of cancer. Even a few years ago, we weren’t sure that such an effect or trend could happen. But now we’re learning about one form of cancer and seeing how that can drive other cancers. For example, Dan Zabransky is an oncology fellow whom I co-mentor with the brilliant Liz Jaffee, deputy director of the Sidney Kimmel Comprehensive Cancer Center at Hopkins, and a pancreatic cancer expert. Dan is extrapolating our aging data in melanoma to pancreatic cancer, under Liz’s tutelage. The way immunotherapy is working in melanoma is being studied by researchers dealing with other forms of cancer, such as pancreatic cancer in Liz’s lab, breast cancer, and colon cancer—the finding that a particular mutation in colon cancer could sensitize colon cancer cells to immunotherapy was made right here at Hopkins, by Luis Diaz, in collaboration with the Vogelstein/Kinzler lab.\textsuperscript{16} In addition, many labs in cancer research are working on various vaccines, which could help with different forms of the disease.

As I look ahead, I’m hopeful because we’re beginning to better understand the conversations between the tumor and the stromal cells and the immune cells. We’re beginning to
understand how to interrupt those conversations when they become harmful to the body—how to block one from the other, how to stop the conversation and make the immune system more active when it needs to be.

The science is speeding ahead, and, in recent years, it’s been accompanied by a better sense of cooperation and collaboration. I find this as encouraging as any particular study. Unlike 10 or 15 years ago, you’re now fully encouraged to submit collaborative grants. The National Cancer Institute advises hospitals and research centers to do this, and the truth is to get a quality paper published these days you need to work together. There’s so much that goes into it that no single lab can possibly do everything all the time. For example, the genomics and sequencing need to be verified and studied in cells and animal experiments. Not all of that is going to be one person’s, one place’s expertise, so you collaborate with others to do the best work.

Look at many of the papers being published today. They often have 20 to 25 authors, and they’re composed of data from three, four, or five different labs. We’ve learned that you can’t do quality science with everyone in their own silos, refusing to work with others. We’ll never cure cancer that way.

If you had told me a decade ago that 20 to 30 percent of melanoma patients—even some with Stage IV melanoma—would be in remission for five to ten years, I wouldn’t have believed it. Even now, it borders on the miraculous to me. But that’s where we are, on the threshold of this new world of research and care.
It’s an exciting place to be. Sometimes, when it comes to the new discoveries and how much our understanding grows day by day, it’s a real race to keep up. Yet then I wonder about what we’re going to learn and better understand come tomorrow, and I cannot wait to see what’s next.

Sometimes I think back to when I was a student, decades ago now, and I was peering through the microscope at what the cells in those petri dish “swamps” were doing, captivated by their movement, their interactions. This sense of wonder and fascination has never left me. It drives me every single day toward the answers.

My infatuation with science has brought me halfway around the world, from Lesotho to Maryland to Philadelphia, and eventually to my lab at Hopkins, where I work with some of the most talented and supportive people I’ve ever known. Our back and forth, our very conversations in the lab, have become as detailed and as dynamic as what goes on moment to moment between the cells in our bodies. Given the political climate we’ve lived through during these last four years, we have had a lot of cause to think about the power of words, and the impact of hate speech. In a way that’s how I think about the conversations that drive malignancy. We’re listening and learning, testing and questioning, and ultimately discovering how to interrupt the malignant conversations when we can, and determining how this disease, which has been documented since ancient Egypt and the pharaohs, can become less and less inevitable for all of us.
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