Preface

I’LL NEVER FORGET THE FIRST TIME I looked through a microscope. I was immediately enthralled by how single-celled organisms in a microcosm can move around, replicate, and interact with each other. That first glimpse when I was 11 ignited a lifetime of curiosity. It’s led me to tackle many of the questions I’m striving to answer today: What are the signaling pathways that drive a cancer cell to change its shape, replicate, or move from one site in the body to another? How does it communicate with the cells around it? A cancer cell is not an island—it doesn’t exist or grow in isolation—so how does it interact with surrounding tissues, bone, and blood? Why does aging impact both the likelihood of a diagnosis and its mortality rate?

Cancer’s resiliency can be remarkable. For example, if you give a normal cell a drug or treatment, it will respond in a predictable manner. But give a cancer cell something that’s supposed to stop it, and more often than not it says, “Oh, this is a problem,” and then takes extraordinary measures to repel whatever obstacle it encounters in order to keep moving ahead.

Through the work in my laboratory at Johns Hopkins University and in others around the world, we researchers
are gaining better understandings about this formidable foe in many of its hundreds of forms. Building on the work of pioneering scientists who came before us, we’re pushing toward better treatments and better outcomes. We have more clues now as to why healthy cells become cancerous and better understandings about the genetic materials present when we’re conceived that can become activated as cancer cells many years later. Following cancer’s trail is rarely a linear pathway. At times, it reminds me of how I found the path to study biology and to work in this field. My life story and my cancer research are often intertwined.

During the last decade or so, I’ve focused my research on revealing how changes that occur as we grow older can alter cancer cells, making them more aggressive—and learning why we become more susceptible to them in our advancing years, specifically as witnessed in melanoma tumor growth. My biggest motivation is the patients, first and foremost. A sobering 1,806,590 Americans were estimated to be diagnosed with a form of cancer in 2020, with more than 600,000 expected to die from it, according to the American Cancer Society, while 17 million worldwide receive the terrifying news from their doctors, according to the World Cancer Research Fund. Cancer isn’t like other diseases. With diabetes, for example, you can exercise to maintain a healthy weight, watch your diet, and take insulin shots to live a normal life. But cancer remains a stubborn disease that we’re still trying to fully comprehend,
let alone control. It still leaves us helpless in many ways. I hate the unfairness of it, and I want to help turn the tide for these patients, their families, and the health care providers who work so hard to save them.

A WORLD AWAY

My fighting spirit and sense of justice have their roots in my childhood. My family left Sri Lanka when I was 2 years old, during the beginnings of what would become a civil war between the Sinhalese government and the Tamil Tigers, a terrorist guerrilla organization that arose in response to discriminatory policies against the Tamil people.

It used to be that when colonized countries gained their independence, most who knew how to run the basic operating systems—water supply, electric grid, transportation infrastructure—returned home, leaving those systems to fall apart because few of the indigenous people had been trained to take over. This is part of what gave the impression that these newly freed countries couldn’t survive without their colonial rulers, further feeding the narrative that the colonized countries were somehow “primitive” and thereby ignoring their rich cultures and capabilities.

My dad’s job was to work in collaboration with organizations like the United States Agency for International Development and the Canadian International Development
Agency to help train the Sri Lankan people to run these systems. Gerald William Weeraratna had a law degree, but he acted more like a diplomat in these times and situations. He helped smooth out that difficult transition from the outgoing colonists to the newly independent countries, teaching the people there how to manage these new systems. His favorite saying was “Give a man a fish, he will eat for a day. Teach a man to fish, he will eat for a lifetime.” (I still have a handcrafted award given to him, of a hand holding a fish with those words inscribed.) I admired him—and now identify with him—so much, because what he was doing sometimes bordered on the impossible, or so it seemed to me, his second daughter and youngest child. He also taught me the importance of my voice, often asking my advice—even when I was only 10 years old!—on the phrasing of the questions for tests he prepared, on current politics, and even on his math.

Dad moved us to Africa in 1972, when I was a toddler. We went first to Zambia, in Central Africa, and lived there for four years before moving on to Lesotho in 1976. That’s mainly where I grew up. Lesotho, a tiny country about the size of Rhode Island, known for its stunning snow-capped mountains and jaw-dropping waterfalls, gained its independence from Great Britain in 1966. Completely surrounded by South Africa, it’s one of only three landlocked independent nations, along with Vatican City and San Marino. We lived in the capital city of Maseru in a lovely rancher that had a large yard leading to
sprawling orchards of apple and peach trees. I used to hide in the branches of a massive willow and read books, totally undisturbed.

South Africa had more resources than Lesotho, and so for anything “extra” we wanted to do, we had to drive ten minutes to cross the border, which had checkpoints and guards. We crossed to go to the mall and for my ballet lessons, among many other reasons. Sometimes it was a fast crossing; we had a pass that made things easier. But other times the wait could last for hours, especially if the guards were in a bad mood and took their time questioning someone in a car ahead of us. It was an unusual and often frustrating way to live, but my childhood in Lesotho was formative in positive ways, too.

Most countries needed some kind of representation with South Africa but were reluctant to put an embassy or officials there because of the negative optics associated with the apartheid government. So, many of these countries had their embassies in Lesotho instead. As a result, the school that I went to, Machabeng College, had four hundred students, but they represented more than seventy nationalities. I feel so fortunate to have grown up with this incredibly diverse population, surrounded and nourished by all those languages, customs, and ways of looking at the world—an experience I’ve continued in my professional life by working with many other immigrants and people from across the United States.

Growing up where I did, amid such diversity, I had a lot of
advantages that I wouldn’t trade for the world. But it was also a period of tremendous upheaval and turmoil, especially in the 1980s, during the last vicious throes of apartheid. As teenagers surrounded by South Africa, we took to the streets to protest the regime’s injustices—I still have a small scar on my chin from a policeman’s rifle butt. A course at our school encouraged our participation in civil protest. All of it made me less afraid to stand up for what’s right, whether it’s for more diversity in the STEM disciplines (science, technology, engineering and mathematics) or making sure that junior faculty have access to the resources that they need. Growing up in such a place, during such times, made me a conscientious but also stubborn person. Only my husband can tell you just how stubborn sometimes! That’s something of which I’m strangely proud.

Around this time, my sister, Sharmila, used to drive me to school. At one point I had a science project growing cultures of dirt and grass in a petri dish; I watched the microcosm evolve over time and studied the growth of microbes daily under the microscope. The cultures smelled simply awful, like miniature swamps. Sharmila called them my “festering hay cultures.” To this day, she’ll say with great affection, “So, what’s going on? How are your festering hay cultures?” Our private joke is a reminder to me that you have to put in the work, even when things are a little tedious, and kind of stink, because the answers are in there. There are no days off when you’re working against cancer. Whatever form it may take, whether it’s dor-
mant or racing ahead, it’s usually trying to outwit you. You have to stay on top of everything going on in your own lab, even the labs of others whose work could influence your outcomes.

Some might compare discovering ways to combat cancer to superheroes battling the bad guys. It’s true that there’s a need to be constantly vigilant and resourceful against the wily, dangerous enemy. Am I waging battles against cancer on a daily basis? Maybe, but they’re often methodical and are won in increments, sample by sample, and data set by data set. But what keeps me going, what has intrigued me for decades now, is how resilient cancer can be. The ways that it can move and “talk” and change constantly remind me how imaginative we need to be in dealing with this disease in all its many forms. We have to respect this opponent.

For example, if you came face to face with an attacker and you were able to shoot him, you’d think that would be the end of it, right? But what if he somehow healed that bullet wound and stood up again? That’s impossible, right? Or say another attacker could magically put his hand over a knife wound to heal it—mend himself so well that he was able to keep on going. Sounds like a superpower a character in a graphic novel might have, doesn’t it? Yet that’s the way cancer often works. That’s the very nature, even the power, of how a cancer cell can transform itself. It fights back.

Such resiliency means we need to think about cancer much differently than we would about other chronic diseases, such
as heart disease or diabetes. With those, we can give someone a bypass or a stent or drugs. Those procedures can prolong a life by years, or even decades. We may someday reach similar measures with cancer—longer remissions and, someday, outright cures, are the goal.

Cancer differs from other diseases in what measures we can take to control it because cancer is much more unpredictable and resistant. What I find remarkable is that it only takes a few cells for cancer to proliferate. That’s a key difference between cancer and heart disease—between cancer and other illnesses. If only a few cancer cells somehow escape treatment or detection, they can cause major problems later on as they continue to replicate into tumors and split off and travel to other parts of the body.

We’re finding now that tumors can leave a primary site very, very early in their life history, before they’re even detected, and go to distant sites and just remain there, waiting. It’s called tumor dormancy, one of cancer’s most disturbing proclivities. And then, as we age, changes in the body drive those tumors out of dormancy and make them grow and metastasize. For example, with melanoma, we can take a biopsy from a 30-year-old who may have early signs of cancer. At this point, those cancer cells may not be that dangerous. But when that same patient is 65, additional changes could occur in those cells that could lead to metastatic melanoma in the lungs—it lies in wait.
TAKING A STAND

From my teenage days in Lesotho, having teachers who urged us to understand what was happening in the world and to act driven by conscience, I learned to be a fighter. The racial strife that has once again erupted in America has triggered some of those memories from my childhood in Africa. That kind of background, growing up in such times, has made me less tolerant of seeing people being treated unfairly. When Nelson Mandela was released from prison in 1990 after 27 years, I felt so joyous that I wasn’t able to concentrate on anything for the rest of the day. I was in college halfway around the world at that point, but I knew his release was not just symbolic—it represented a sea change, one that had been a long time coming.

I had a philosophy class in high school titled the Theory of Knowledge. A quotation from that class that has stayed with me is Mahatma Gandhi’s adage: “Be the change you want to see in the world.” One of my favorite classes back then was community service. For that we did things like digging ditches to slow erosion and going to villages to help fit people for eyeglasses or administer vaccinations. Social justice and social work were activities that many of us in that class did together. We were proud to take up a social cause, to take a stand. These classes shaped my world view.

But while I look back on our time in Africa as my great adventure, there were minuses, too. If I saw a tin can on the
road or a paper bag, I knew that I shouldn’t kick it because there might be a bomb inside. I learned that if I saw a car parked alone on the side of the road, I should cross the road and not walk next to it, because it might have an even bigger bomb inside. I suppose it’s similar to the United States, where kids know that if an alarm sounds in school, they need to huddle in a corner, sheltering in place because there might be a school shooter. Dangers arise in many places.

Years ago, I was in Edinburgh, Scotland, visiting my brother, Tino, and his family. It was my first visit there and we were walking around Edinburgh Castle, when the cannon went off, which it does every day at noon. I grabbed my niece and nephew, threw them to the ground and covered them with my body. It was instinctive. But my relatives were baffled, thinking, “What on earth are you doing?” It was my past coming back to life. Yet how does one fully explain something like that? How do those reactions become hardwired? In a way cancer cells are like that—programmed to survive and respond to their environment, and learning ways to adapt to it.

A FASCINATION WITH SCIENCE

Where I was in the family birth order must have had an effect, too. I’m the youngest of three kids. My brother and sister are much older—I’m the baby in the family by a good seven years. When we were living in Zambia, and my brother and sister reached high school age, my parents decided that the local
schools there weren’t strong enough. In that way, my parents were typical South Asian parents: education was the only thing that mattered to them. So, my brother and sister were sent to boarding school in the United Kingdom. For a time, they were like cousins who came to visit during the summer holidays. It was hard, because I was very attached to them, and particularly idolized my big brother, Tino, with whom I’ve always had a special relationship. Four-year-old me would always pack a bag for myself (books, a night dress, toothbrush, and snacks) to accompany him to the airport, hoping against hope that somehow, this time, they’d let me on the plane with him. To this day, my siblings and I are extremely close, even though we are continents apart.

Being on my own while they were away at school taught me the importance of being independent. Even now, though I work with amazing people in my lab and I’m surrounded by a loving family, I’m comfortable being on my own. I didn’t mind being an only child much of the time, pretty much left to my own devices. Eventually, my brother moved back to Africa with his wife for a time, and my sister moved back as well, and for a short period we were all together. This was when I was 13 and my sister often drove me back and forth to school. That’s when we first discussed those “festering hay cultures.”

My mother, Carmen Lorette Wickramasinghe, was a strong, independent woman. Her mother, Grace Tucker, was the product of European colonialism—half English and half Portuguese. Her father, Leslie Wickramasinghe, was an aristocratic man
whose vice was playing billiards in his local country club. He died of cancer before I was born, as did my mother’s only brother. As for my mother, I’m told that she was an absolute rascal growing up. All the boys were afraid of her because she had a gorgeous older sister, and Lorette would beat up any boy who gave her sister grief. She was captain of the neighborhood boys’ rugby team when she was 16. Most girls of the 1950s gravitated toward more genteel sports.

Just two years later, at 18, my mother married my father and then gave birth to my brother a year later. Even though she wasn’t expected to go on to college, she always valued education. Her uncles were world-renowned astrophysicists, one at the University of Oxford and the other at the University of California, San Diego. She came from an academically rich, scientifically oriented and accomplished environment, but back in the 1950s girls weren’t expected to pursue much along those lines.

When I came along and proved to be a good student, Mom was all over that, making sure that I did my homework and helping me prepare for exams. She always told me, “You can do anything you want, but you need to stand on your own two feet. Never depend on a man. Never.” She told me this even though she loved my father dearly. Still, she was of the mind that life, at least my life, was not just about getting married and having babies. “Your life is to go out there,” she told me, “and do something big.”
Like a lot of people who go into the sciences, my favorite class was biology. It has been my great love all my life. The subject became even more important to me after my favorite ballet teacher died of cancer. I had begun dancing when I was 3 and continued until I was 16. Sticking to the strict regimen of ballet taught me that when you really love something, putting that level of work into it can be a real joy. I was serious about it and was very close to my instructor, Carla De Bruyn, a white South African woman who came across the border to teach us. Despite growing up in a small town in South Africa, Carla had a class of every color of kid you can imagine, given the diversity in Lesotho. She wasn’t afraid to dream big about what we could do.

I remember her arguing with my mum. At first, my mum thought the dancing was cute and good exercise for her chubby daughter. As I grew older, and spent three hours a day practicing, she told me I had to drop it, so I could focus on my studies. Anyone who’s pursued an international baccalaureate in high school or had a child who’s done it knows it isn’t easy, and now I kind of see my mum’s point. Yet Carla stood her ground in supporting me, too. In the end, she convinced my mum to drive me ninety minutes each way, three times a week, to go to a dance class across the border in South Africa. Carla had a higher-level class there, and she felt I was ready for it. As a mother now, I admire my mum’s devotion to cultivating my interests, even for something she didn’t agree with, simply because I loved it.
When Carla became ill and then died of colon cancer in her fifties, I was devastated and decided that I needed to know more about this disease that took her from us, along with my uncle and grandfather. Because Maseru was the capital, it had a British High Commission nearby, with a good library. Probably to my mother’s relief, after Carla’s death I became a regular visitor there. The librarian helped guide my interests by showing me TV specials about science, even though I was an audience of one.

My favorite was “Life on Earth,” a BBC series. Presented by David Attenborough, the show went all around the world, detailing animal life including the mountain gorillas in Rwanda that Attenborough encountered in Dian Fossey’s sanctuary. My favorite episode was about how whales feed. They make a huge circle and form a cylinder that fills with fish. That allows the other whales to come in and eat all the fish. I thought that was so cool. The show offered me a glimpse of the worlds that existed well outside our landlocked country. By watching those programs and going through that library of books, I began to dream about what I could see and even do in the bigger world that lay beyond the border we crossed every day.

I became a heavy reader. I spent hours in the library, and I eventually worked my way through its entire collection of encyclopedias, along with lots of National Geographic issues. My mum used to call me the “Encyclopedia Lesothania,” instead of the “Encyclopedia Britannica,” because I would
recite endless bits of knowledge. Today, I’m still pretty good at Trivial Pursuit, though I’m not sure how well that’s served me.

What that time in the library did was allow me to dream. Leafing through all those books, learning as much as I could about the world around me, and about the disease that took Carla so prematurely, eventually led to the idea of pursuing a career in cancer research. By the time I was 16, I had decided that I would run my own laboratory one day. And I knew that the best place for that, where the best work was happening, was the United States.

**COMING TO AMERICA**

Of course, it’s a long way from Maseru, Lesotho, to St. Mary’s College in southern Maryland, where I completed my undergraduate studies—8,139 miles to be exact. Even though my brother and sister had gone to school in the United Kingdom, I was adamant that I needed to go to college in the United States. At first, my parents wouldn’t hear of it—they were absolutely horrified when I first brought it up. Their vision of America in the 1980s was that everyone was on drugs and carried guns. There was no way they were allowing their youngest child to go there alone. Still, I knew that the best medical cancer research was being done in this country. “That’s where I’m going to go,” I told them and dug in my heels, which led to one of the very few major fights I had with my father.
Despite their objections, I laid out all my arguments about how the best programs were in the United States, but my dad wanted me to go to Oxford or Cambridge. And on and on we argued. Still, I believe my parents, especially my father, were impressed by the research I had done about college—how I was clearly stating my case about a subject that was near and dear to both of them—education. My dad believed it was the great equalizer, that if he could educate everyone around him then they’d all have an equal shot at a good life. In my own way, I believe that, too. To become a fisherman, so to speak, I knew I had to go to America to pursue my studies.

Finally, Mum and Dad said I could go but that I needed to enroll at a college close to friends. We had family friends, the Sengamalays, in Washington, DC, and even though it can be a two-hour drive or longer in traffic to where I ended up, my parents agreed. Further complicating things was that I wasn’t 18 yet, so those friends needed to become my guardians, too. Over the years they and their two boys have become my family here, and that means so much more than I can express.

So that’s how I ended up attending college at a small, beautiful, completely rural campus of maybe fifteen hundred students located on a peninsula extending into the Chesapeake Bay—a far cry in every way from landlocked Lesotho. It helped that St. Mary’s College had been so persistent in recruiting me. I had also applied to George Washington, Vassar, and Hamilton, but St. Mary’s had so few international students
that it needed more. They called and called, and my mum said, “Oh, they really care about you.” As it turns out, they did. I’m still great friends with Rich Edgar, the admissions director at the time, and now the college’s director of development. I lived with his beautiful family on their farm for a couple of months after graduating, and they joke that they still refer to their guest room as “Ashi’s room.” They also taught me how to use a vacuum cleaner, an Amish drill, and many other useful skills. Going to St. Mary’s is one of the best decisions I ever made, and it proved to be an amazing experience. It was my first real step into a field in which I very much wanted to have a major role. One of the key things the college did was to arrange summer internships in laboratories; I worked at the University of Maryland in Baltimore and also at the university’s Chesapeake Biological Laboratory on beautiful Solomons Island close to the college. Those internships were vital in cementing my interest in a research career.

That said, my experience was also shaped by being one of only a handful of kids of color on campus at the time. And I was a foreigner—no one else on campus had an accent like mine, and my classmates and teachers didn’t really know what to make of me. I adapt very easily, but some of my classmates—maybe not so much. I found it more amusing than anything else when people would ask me, “Do you ride elephants to school in Africa?” At first, I’d try to educate them, but sometimes—I hate to admit it—I’d just make stuff up. “Of
course, I ride an elephant to school back home,” I told them. “In fact, I’ve got a few in the garage.”

Other than that adjustment, and maybe, in part, because of it, St. Mary’s was exactly the right place at the right time because it allowed me to be absorbed by American culture. Everyone was so warm and friendly and embracing. Still, I had no clue about American culture at all, especially as a young adult. I remember my first couple of days in college. All the girls would sit in the hallway outside of their rooms and they would talk, getting to know each other. I would be in my room thinking, “Oh, I really wish I could join them.” I thought someone had to invite me. That’s how it would have been in my British-leaning culture, the way I was brought up. Finally, one of the girls saw me in the bathroom and asked, “How come you never sit in the hallway with us?” I didn’t know it was that easy to join them.

Because I had graduated from high school with an international baccalaureate, I went straight into upper-level biology classes at St. Mary’s. There were some struggles early on. I hadn’t taken many multiple-choice tests before coming to college, which really threw me. And I was docked points for using British instead of American spelling. My biggest disaster was flunking organic chemistry. That was the first course I had ever failed, and given how critical it is to a career in the sciences, it was a big setback to overcome. Yet, through it all, I loved my classes, especially those having to do with biol-
ogy, and I graduated in three years. I knew I’d made the right choice in studying this field.

After graduating from St. Mary’s in 1991, I came to Johns Hopkins for the first time, becoming a senior technician in the school’s oncology center. My mentor there was Bob Casero. He took great care of all of us who worked for him, and through him I began to see the role I could play in medicine, that it would be a mixture of doing important research and being able to mentor and foster others—by running my own lab someday. The idea of running my own lab had been with me since high school, but at Johns Hopkins I began to envision how to make it a reality.

Still, I must have had one of the worst first days on the job ever at Hopkins. I had broken my foot when a horse, a Persian workhorse (from the Edgars’s farm), which are simply huge, had stepped on it. So, I showed up on my very first day in a cast. And things went downhill from there.

We were looking at an experiment on a UV box. It had a dish of water, with mutagen in a solution for a project about DNA. You turn out all the lights, put on a plastic shield, and, turn on the UV box. So, I went into the darkroom with the director on the project, my other boss and mentor, Paul Celano. He said, “I’m going to turn off the light. You pick up the plastic shield and put it on your face.” In the dark, I picked up what I thought was a plastic shield. I brought it up to my head, and it went “Splash!” It wasn’t the shield at all. It was the container
full of staining solution. As the lights came on, my boss saw me standing there—all wet. That’s when I just dropped the now empty container all the way over my soaked head. He shook his head and said, “Probation period: three months.”

Of course, the story is now legend, part of my origin story. When Bob Casero introduced me for my chair, my current position at Johns Hopkins, he said how proud he was of me, and how I had “learned new ways to image DNA” when I was in his lab.

Despite some missteps and mistakes along the way, I’ve always been comfortable in the lab. In many ways, it feels like a second home, where I should be. Many days I’m as excited by what I’m witnessing as I was at the age of 11, peering through that microscope for the first time.

When you’re a woman, you sometimes receive conflicting messages about how far you should or can go in medicine. The messages might be something like, “Maybe you shouldn’t go on to grad school. Stick with what’s easier.” Early in my career, someone told me I was more suited to be a technician, that I probably shouldn’t pursue a PhD—it might be too difficult, too much, for someone “like me.” Both a professor in college and a professor (at the time) in the very department I now chair told me not to bother with graduate school. Even later in my career, there were points where I was told I wouldn’t be allowed to continue. Being a woman of color made it no easier—I often had to fight for everything from recognition for my ideas, to a
seat at the table, to promotions and advancements. But in sit-
uations like that, my stubbornness is an asset, and I’ve always
known in my heart that this is where I belong, even if it means
that others not used to people who look like me aren’t comfort-
able with it and need to overcome that to make space for me.

Thankfully, I had people around me who were giving me
more positive messages, about how I could—how I should—
keep going further. And, over time, that became an important
part of my personal philosophy. What more could I do, espe-
cially when it came to understanding cancer?

This curiosity and fascination with the world, first
glimpsed back in Lesotho, took me from my graduate studies
at the George Washington University to Johns Hopkins, the
National Institutes of Health, the National Institute of Aging,
The Wistar Institute, and back to Johns Hopkins. What more
can we learn, discover and, ultimately, accomplish when it
comes to cancer? In recent years, we’ve made great strides,
many of which I’ll tell you about. Much has changed for the
better in recent decades. Our research is branching off into
what were unseen directions only a few years ago. When it
comes to cancer, the level of cooperation and understanding
is now worldwide—a true international effort.

Undoubtedly, what lies ahead won’t be easy. But coming this
far wasn’t, either. Managing or controlling cancer? Making sure
a diagnosis doesn’t become a death sentence? For me, there’s
no more captivating or challenging task right now in medicine.
This page intentionally left blank