Is Cancer Inevitable?

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CHAPTER 2
The Role of Cancer Research

WHEN I WAS STUDYING CANCER in graduate school, I often thought, “Oh, my God, what are we dealing with here?” I learned how a cancer cell when treated with toxic drugs can build a “pump” on its surface to push the drugs back out. This multidrug resistance is now a well-known, well-characterized phenomenon. I watched the chromosomes inside cells break when given an over-the-counter chromium diet—broken chromosomes meant damaged DNA, and damaged DNA meant a tee-up for cancer. I watched melanoma cells morph into structures that look like blood vessels, a process called “vascular mimicry.” Anyone who goes into cancer research has this epiphany, often multiple times over—where you’re in awe, but you have a degree of trepidation, too, as you realize how cunning cancer is, and what measures must be taken against this opponent.

We’ve learned how adept cancer is at spreading throughout the body. Sometimes, the cancer is confined to a particular organ or area; in more cases the tumor will be detected in, say, the breast, but by the time a diagnosis is reached, the cancer
will already have spread to other areas—the lungs, the bones, the brain. Even if we’re able to determine whether the cancer is localized or has spread, it can be a fine line between what is too little and too much for a cancer patient to bear, especially in the pursuit of finding and ridding the body of every cancer cell. If that isn’t done, the cancer almost always returns and the patient suffers a relapse.

In the mid-1960s, a small group of doctors treating leukemia in children decided to test the limits in that area of cancer research. Sidney Farber, the father of chemotherapy, had great success at Children’s Hospital in Boston treating kids with leukemia with a folic acid–blocking agent. It was the first time a drug tested as an anticancer agent proved effective against leukemia. Despite such progress, Farber was reluctant to give children higher or potentially more dangerous doses. In addition, he resisted giving kids several chemotherapy drugs at the same time. “I will not injure two children to save one,” he said. So it was left to other doctors in this field—Donald Pinkel, James Holland, Tom Frei, Emil Freireich, and others—to push the envelope when it came to chemotherapy. They began to prescribe such drugs increasingly in combination, what we call the chemotherapy “cocktail” today. “To really do the job, you need a combination of agents,” Pinkel said. “Using them two, three, four at a time. That was a very fundamental observation and fundamental insight. It became key to our progress moving forward.”
For a few years in the 1960s, these cancer doctors were together at the Roswell Park Hospital in Buffalo, New York. Even when Pinkel left to establish St. Jude Children’s Research Hospital in Memphis, the group still gathered several times a year. In part, that was because they were receiving so much criticism from their peers and the rest of the medical community about their new approach. “To many in the medical establishment, we were seen as reckless or even irresponsible,” Jerry Yates said. “That resulted in many of the names that they called us—killers, poison pushers, renegades, pirates, cowboys. For a long time, we were shunned, ostracized by the rest of our world. That’s how far out of bounds, even dangerous, we were perceived to be by others.”

Despite the harsh criticism, these “cowboys” continued conducting their clinical trials and publishing their reports, and eventually they took childhood leukemia from the 10 percent survival rate it had a half-century ago to the nearly 90 percent survival rate it has today. They are now recognized as cancer pioneers, and their success is a perfect, inspiring example of how research can lead to defying what seems to be a nearly inevitable, tragic outcome for thousands of families.

PAYING MY DUES

Early in my career at Johns Hopkins, as a technician in the oncology center when I was barely 21 years old, it began to dawn
on me that with cancer it isn’t necessarily the initial tumor that kills you. Rather, it’s how cancer can metastasize and spread throughout the body. I became fascinated with how cells move—what draws them to different sites. In addition, I realized that to do the kind of work that I wanted to do, I needed to go to graduate school.

Although as a woman during a less equitable era I’d received conflicting messages about far I could or should go in medicine, when I told Bob Casero, my boss at the Johns Hopkins Oncology Center, that I wanted to run my own lab someday, he couldn’t have been more encouraging. Now I realize how unusual that was—perhaps still is. Bob confirmed that to go down this path, I’d need to attend graduate school, and he then helped me through the application process and wrote a recommendation. He urged me to talk to as many people as I could and learn about everything that was out there. He’s been in my corner ever since.

Early on in that process, I was talking with another doctor—a gruff, old-fashioned guy, and he asked why I thought I needed a PhD. I told him how I was really interested in cancer research and how deeply I felt about the oncology patients with whom I’d worked. I told him how I had read books to the kids in the oncology ward at Johns Hopkins, and how much their plight touched me.

“Well, why don’t you just become an MD?” he replied.

At first, I didn’t know what to say. So I was honest and said,
simply, “I don’t have the emotional strength to do that on a
daily basis. I need to bring about change for them from behind
the bench.” He looked at me and said, “That’s one of the best
answers I’ve ever heard.” From then on, I knew to embrace
my authenticity and be honest—be myself, for better or worse.

Around this time, Hopkins changed its rules for visa appli-
cations and procedures. I was in the United States on an F-1
student visa. I couldn’t file for my green card as a techni-
cian—I had to be in a more senior position. By the time this
happened, I’d missed all the application deadlines for doctoral
programs at Hopkins and the vast majority of other schools.
Then a strange thing happened.

I was going home one evening, feeling very discouraged
about the visa and the graduate school situation, and when
I got to my door found a flyer from George Washington
University. I don’t know whether someone, maybe a GW alum,
slipped it under the door—there were a lot of students in my
building, after all. However it got there, I was glad to get my
hands on it. I couldn’t believe it when I saw that they were
offering rolling admissions and accepting students through
June. They had a new PhD program in molecular and cellular
oncology, which sounded tailor-made for me.

I applied and got an interview, which I’m pretty sure was
because eminent scientists like Bob Casero and Bert Vogelstein
wrote recommendations for me. In fact, when I went to
Washington, DC, for the interviews, several of the professors
there really only wanted to talk about Bert and the landmark work he was doing at the time! A little background is called for here. In the early 1990s, Bert and I once worked at the same location down on Bond Street at Hopkins. The building was an old grocery store that had been converted into labs. Bert was the first to unravel the genetic evolution of colon cancer. His identification of mutations of a gene known as p53 in colon cancer began a tide of research linking alterations in the gene and other cancers.\[^6\] In 2003, he was ranked as the most highly cited scientist in the world during the previous 20 years.

During this time, I was also taking classes at the School of Public Health—in the department I now chair, ironically. One of the courses I had was in molecular carcinogenesis, and Bert was scheduled to be a guest lecturer in that course. I went to class that day, and the other students and I waited, and we waited, and we waited. But Bert never showed up. And I thought, “Wow, that’s so uncool. Guess some people just think they’re too big for their shoes.” If you know Bert at all, you know how wrong I was about that! Remember this is the man who dedicated every textbook he ever wrote to his trainees, only accepts talks if trainees invite him, and so on. But back then, I didn’t know him at all.

I was so mad that my sense of injustice got all fired up. I fumed all the way back to the lab. I had to go to a different room to develop the experiment I was working on, and when I walked in, there was Dr. Vogelstein, as I called him then.
“Oh, you’re here?” I exclaimed.
“Excuse me?” he replied.

Now, you need to know this was the first time I’d ever talked to Bert Vogelstein. He didn’t know me from a bar of soap.

I said, “Well, I just want you to know that there was a room full of students who were extremely disappointed you didn’t show up. I’ve never seen students wait so long for a professor.” Then I turned and left. (I’m a lot less impetuous these days.)

The next morning, I came into the lab, and as soon as I came through the door, someone said, “Bert Vogelstein has been here three times looking for you.”

“Oh, God,” I thought, “What have I done? I’m going to get fired.” But I decided I might as well face the music, so I went across the hall to find him. He was just walking in to find me, and the first thing he did was ask my name. Then he said, “I just want you to know what happened. The invitation to your class had the wrong zip code. The envelope arrived the day of the lecture, and my assistant knew I wouldn’t be able to do it, so she just put it away. I had no idea.”

Bert went through this whole long explanation, and all the while I’m thinking, “Oh my God, you’re Bert Vogelstein, why are you explaining yourself to me, a 20-year-old technician?”

But I kept my mouth shut. I let him go through the whole explanation.

At the end, I quipped, with a naughty smile, “OK, but don’t let it happen again.”
Bert cracked up, and so did I, and he’s been my supporter and mentor ever since, guiding me through each transition of my entire career, to this very day. Many years later, when I got engaged to my husband, who had been a postdoctoral fellow in his laboratory, he quipped, “Well done, man; you’ve got a lively one there!” I think he was just too nice to say, “Good luck, you’ll need it!”

So, I got accepted to George Washington University, and I began classes there late in the summer of 1994. From the beginning, I knew that I’d landed in the right place. I did my first rotation in the lab at GW, and I liked it so much that I told my advisor, who was also the head of the program, that I wasn’t that interested in doing the usual rotations in multiple other laboratories. I just wanted to stay here, in the lab; he said, that’s fine, and that’s what I did.

Steve Patierno was my mentor at the university. We called him “Papa” Patierno because we were like his kids, and he always kept an eye out for us. It so happened that I was one of two people in his laboratory not working on chromium-induced molecular carcinogenesis, which is how cancer forms in the body upon exposure to chromium. As a result, I was able to focus on metastasis, which was where I wanted to be. From there I became particularly interested in the microenvironment because of how it guides metastasis. And to do that, I needed to understand how cells signal each other—the intracellular signaling we discussed in the previous chapter.
more I explored all of this, the more I became convinced that our bodies are hardwired somehow in this way and that the metastasis side of research was where to be.

After graduating from George Washington in 1998, I became a postdoctoral fellow at the Johns Hopkins Oncology Center. I had been working on prostate cancer since graduate school and was excited to postdoc at Hopkins with John Isaacs, a world leader in the field of prostate cancer. I thought that prostate cancer was going to be my specialty, where I’d make my mark. That’s what I thought until Jeff Trent came into my life.

At the time, Jeff was the scientific director of the National Human Genome Research Institute at the National Institutes of Health in Bethesda, Maryland. He was a pioneer in the field of microarray design and pharmacogenomics, which is the study of how genes influence a person’s response to drugs, and how drugs affect gene expression. This was all really new and exciting back then. After hearing his talk and seeing how kind he was to me in a meeting, I knew that I wanted to work with him and learn more about that field, too.

When I got to his lab, I told him, “I’ve been working on prostate cancer since grad school. I’d like to continue that.” Jeff replied, “Well, the only problem is that I hired you because you’re a cell biologist. And there’s a new project I need your help on. If you want to come back to prostate cancer, it’s fine. But for right now, I really need your help with this.”
That project became our landmark study about Wnt5A in melanoma. Wnt5A is one of a family of proteins that can influence much of how the body reacts and deals with cancer. The Wnt family, and specifically one member of that group of proteins, is key in allowing melanoma cells to resist therapy. It can also allow the cancer to leave the primary site and travel to metastatic sites elsewhere in the body.

It’s funny. If Jeff hadn’t said I could go back to prostate cancer at some point, who knows what would have happened. Would I have taken the job, this work that changed my life? I don’t know, but I’m glad I did. Jeff taught me the value of collaboration, and working for him introduced me to melanoma research; that’s where I’ve stayed ever since.

His lab had compared the gene expression patterns of melanomas that responded to early forms of immunotherapy to those that did not, using microarray technology. Jeff wanted me to do a follow-up study to see how different gene expression patterns were potentially impacting metastasis, how all of this was affecting therapy resistance, different outcomes in patients, and how much of this hinged on the Wnt5A gene. It turned out to be a fascinating protein and a career-changing project. In many ways, we’re still at work on these developments and insights today.

I joined the lab on October 2, 2000, just after I’d turned 30 and gotten engaged to my husband, Pat Morin. New job, new decade, new life. That’s enough for now, right? But the world
wasn’t done with me quite yet. Three days after I took the job and began to commute from Baltimore to Bethesda, my dad passed away in Sri Lanka. (My parents had moved back there from Africa just that year.) As you know, I was really close to my dad. And it was very sudden. He was only 66 at the time. Unfortunately, he was a heavy smoker, and he had a triple abdominal aortic aneurysm. In the Western world, he might have survived that. But in Sri Lanka, 20 years ago, it was too quick, too much.

For someone like me to leave the country under those conditions isn’t easy. To unexpectedly be called home can be complicated when you’re an immigrant, because every time you leave the country, you need to have your visa papers in order. Since I had just started at Jeff’s lab, much of my visa paperwork was up in the air. Thankfully, Pat took care of the details, while I crumbled under the news. We met my brother and sister in London and then flew together to Sri Lanka. When I returned to the United States, Jeff was there for me, too. I’d been working in his lab for only two days when my father died; then I’d been gone for nearly two weeks, with the time it took to get to Sri Lanka and back. So once we got back to Baltimore, I went straight to work the next day in Bethesda. Almost as soon as I came in, Jeff saw me and asked, “Why are you here?”

And I thought, “Oh God, he’s firing me now. Because I disappeared for two weeks.”

I jumped in with, “It’s okay, I’ll get to work. I’ll work really hard.”
And Jeff said, “No, I want you to go home. You’ve had a major life event. You need to process this, and you’re not going to do it here.”

We argued, with me insisting that I needed to stay—that work was the only way I could take my mind off what had happened. In the end, we made a deal. Jeff let me handle it my way, but he insisted that moving forward, the two of us would go out to lunch on a regular basis. He wanted to know what was on my mind, how I was working through this, how I was doing.

At first, I didn’t think anything of it. I worked that day in the lab and was back again the next morning, eager to settle into some kind of routine. Yet a few weeks later, Jeff reminded me that we needed to catch up over lunch. He did this even though he was so busy at the time. I mean, he was the scientific director of the National Human Genome Research Institute! Right when they had just finished sequencing the human genome project! Every time you stepped off the elevator, there were reporters everywhere. We ran into Mike Wallace several times. It was just crazy.

Still, Jeff made the time, and whenever he took me to lunch, we didn’t talk that much about the science. He wanted to hear about my dad. The work that he had done in Africa and elsewhere. I told him silly anecdotes, like how when I’d first started working at Hopkins as a young tech, my dad bragged about his daughter at Hopkins to everyone whom he met, even though I was basically just washing the dishes at the time!

Years later, when I was offered my current job at Johns
Hopkins, I called Jeff to ask what he thought. What was his advice? Was this the time for me to move? Was I ready for this level of a leadership job?

The first words out of Jeff’s mouth were, “Oh, Ashi, Hopkins? All I can think is how proud your dad would have been.” I couldn’t believe he remembered my little anecdote how absurdly proud my dad was of my technician job at Hopkins, and it took me a few minutes to stop crying. I am so lucky—caring mentors like Steve, Bob, and Jeff have been the buttresses of any success I’ve had.

**CANCER RESEARCH AS FOUR-DIMENSIONAL CHESS**

As I said, I was planning to return to research in prostate cancer at some point. Yet in Jeff’s lab, I became more intrigued by the work we were doing with the Wnt family of proteins. This is what eventually led me to the study of melanoma.

Compared with other areas of research in cancer, the field of melanoma was so embracing and inclusive. It didn’t matter if you were a man or a woman, white or a person of color. My colleagues were a diverse, engaging group of international and domestic researchers. Everyone was so friendly and collaborative, an atmosphere created by the leadership at the time, specifically Meenhard Herlyn, who later became my close friend and colleague at The Wistar Institute. To this day, some of
my closest friends and best collaborators are people I’ve met through this community.

The science was as stimulating as the community and the company. In my lab at the National Institute on Aging, we began to study a fascinating phenomenon in melanoma that runs counter to much of what we had understood about cancer up to this point. In a lot of cancers, if a tumor grows fast, it’s also very aggressive. In melanoma, what we see is that tumors that have rapid growth tend to be less effective at leaving that primary site and metastasizing, going to other parts of the body. We call this the “Grow or Go” paradox, where a melanoma cell that otherwise has all of the indications of rapid growth tends to have fewer indicators of invasion, and vice versa. This isn’t what we expected to find in our research several decades ago. That’s what makes this family of proteins, the Wnts, so interesting in how they can influence cancer development. We started to realize that these proteins are absolutely critical—both in the early stage of the tumor as it begins to grow and develop, and in the later stages, when it leaves the primary site of the skin to invade the body. Through our studies of Wnt, we started to understand how different members of the same family of genes could play opposing roles, and yet both contribute to tumor progression.

In Jeff’s lab, we had investigated Wnt5A, a member of that Wnt family. At that time, and even to this day to some extent, when you mention the term Wnt, most people’s minds jump
straight to the best-known mediator of Wnt signaling, a protein known as beta-catenin. Beta-catenin was made famous for its roles in colon cancer, in a paper out of Bert Vogelstein’s lab that has been cited thousands of times.9 The lead author of that paper, Pat J. Morin, was the man I would later marry, and he was the first to identify activating b-catenin mutations in cancer. But my work on Wnt signaling showed something different—not only did Wnt5A not activate beta-catenin in our melanoma systems; it actually suppressed it, through a different mechanism that did not involve its usual degradation pathway.10

Back then, this was uncharted territory for those of us in the field. Until this point, Wnt5A hadn’t been associated with melanoma at all. Further studies from my laboratory have shown that this molecule is a key driver of metastasis. Wnt5A is critical in fostering changes in the cytoplasm’s network of protein filaments and promoting different ways of invasion, ways we hadn’t even considered nearly two decades ago. Others in the field are now also finding Wnt5A as a critical mediator of therapy resistance.

Our report was titled “Wnt5A signaling directly affects cell motility and invasion of metastatic melanoma.” Although we’d presented the data publicly several times previously, the major presentation was scheduled for the American Association for Cancer Research meeting, which is held annually.

Until this point, the Wnt group had been seen as a signaling pathway for cancer, a family of proteins that drives cancer
growth. And now here we were saying it didn’t work that way with melanoma—Wnt5A didn’t lead to a high proliferative/low invasive situation. In fact, it was the opposite: Wnt5A disables the beta-catenin pathway, slowing the cancer’s growth but resulting in the cancer becoming invasive, much more prone to metastasis. Like anything that runs counter to prevailing opinions and beliefs, some people were intrigued by the new findings, while others got pretty upset about them.

Before our research, Wnt5A had largely been studied only in frogs. Randall Moon at the University of Washington outlined how it was a driver of the way frogs develop and the way that vertebrae line up and the embryos are formed.11 It hadn’t been fully studied in human beings, but that didn’t stop some in my field from refusing to consider our data initially. Those people would say, “Wait a minute. It’s a Wnt protein, so it must be driving growth.” They insisted that if it’s a Wnt, it should activate beta-catenin and be working through those pathways in the body. It was so new that not everyone could wrap their minds around it.

In looking back on it, we had a very naïve view of what these proteins can do, and the more we learn about Wnt5A, the more it surprises. At first, we thought that Wnt5A drove metastasis, end of story, but now we know that there is much more to it. Not just the expression of Wnt5A but where and when it is expressed are critical for tumor metastasis. For example, it’s now known that tumor cells leave the primary
site early and go to distant organs, like the lungs, and then just sit there for years, in this slow cycling state. Multiple changes can occur that then bring those cells out of that dormant state, and they start to grow. When that happens, they can soon become a problem, with large metastatic outgrowths to which patients eventually succumb. This emergence from dormancy can involve everything from secreted growth factors to changes in the immune system.

With melanoma, we’ve learned that this Wnt signaling pathway plays a huge role in driving such movement, via this “Grow or Go” paradox. Melanoma cells can switch between high proliferative / low invasive and low proliferative / high invasive phenotypes, which is guided by changes in Wnt signaling. So, cells need to stop growing and start going to leave the primary site, but when they get to the distant organ, they need to pause and make sure they can survive that new environment.12

In the lab, we began to see that a cancer cell that’s multiplying rapidly, driven by beta-catenin, has a lot of antigens, the substances that cause the immune system to produce antibodies against what it has determined to be an intruder or invader. Antigens can get presented as red flags to the immune system on the surface of the cell. In other words, the immune system doesn’t recognize the cell’s products and sees them as foreign. In essence, they’re signaling to the immune cells to come in and attack. But we found that Wnt5A can shut much of that down.
In doing so, Wnt5A can hide the tumor from the immune system very effectively. It’s part of how it helps the cell survive its new environment. Our most recent work is leading us to realize, though, that changes in that new environment eventually conspire to suppress that Wnt5A-driven dormant phenotype, and drive reactivation of the “grow” program, such that those cells start to grow out again, forming large metastatic outgrowths.

Someone once said that cancer research can be like playing three-dimensional chess. But our work, and that of others reveals that it’s at least four-dimensional chess—with time being a critical piece of the puzzle. I will always be grateful to Jeff for letting me take the Wnt5A story and pursue it as my own research. Had he not left the National Human Genome Research Institute to move to Arizona, I would have loved to continue pursuing that work with him. But that was not to be, and when he moved to Arizona, I accepted an offer from the National Institute on Aging.

MOVING ON TO THE NATIONAL INSTITUTE ON AGING

In 2004, I became a staff scientist at the National Institute on Aging (NIA) in Baltimore. Even though I struggled with some of the personalities there and the machinations required just to get my job done (many a night I drove home after work in tears),
during my eight years at NIA I began to explore the important role that aging plays in cancer. While I didn’t actually work on aging during my time at NIA, this is where my interest in aging’s influence on cancer, specifically melanoma, took off, thanks in part to conversations with Dan Longo, our brilliant scientific director at the time.

Working at the NIA was challenging. I wasn’t on tenure-track, and to earn my keep if you will, I helped to manage a large laboratory that focused on research that was beyond my area of expertise. What kept me going there was my own tiny group of three or four people. We did the research I was interested in, and I was able to write senior author papers and have them published. Our work was becoming more recognized, especially in the international melanoma community. I had once thought that cancer research would always be kind of competitive, which at times turned me off. Yet the international melanoma community continued to win me over with their offers of support and collaboration. I was now, and have remained ever since, Team Melanoma, my prostate cancer study days long forgotten.

Despite the challenges at NIA, there were so many positives, from wonderful colleagues to being exposed to people like Judith Campisi and her work on senescence. A senescent cell is one that basically stops growing but doesn’t die. It may seem like these kinds of cells are just sitting there, but they’re in fact secreting several different factors that are crucial to
cancer development. Judy identified that what these cells are secreting can be a double-edged sword. Some of them are immunological factors and can be tumor suppressive. But others act as signals to the cell to metastasize and/or grow.\textsuperscript{13}

Over the years, we found that there are very different types of senescence. One of the types that my lab identified a few years ago was called “pseudo senescence.” That’s when the cells look like they’re senescent—aging, becoming more inactive—but they can be very invasive. They can metastasize to different sites, and as we age these processes become more pronounced.

That aging would have a major influence upon cancer seems a bit obvious today, but we never really thought too deeply about it until a few years ago. The microenvironment—what’s happening around the tumor and how it affects the tumor—has become a major part of my thinking and research philosophy. So much so that I believe that it also applies to the world and people right around you, around each of us—your actions, your decisions, the way you respond to things. In many ways, our very behavior with regard to our immediate surroundings can function like cells in our body.

While I’d never thought about aging and cancer that much until I took the job at NIA, once there, with everybody around me working and thinking about aging, I thought, “Wait a minute, maybe all of these aging changes that are occurring normally drive the aggression of cancer as a disease of aging? Let me look at that more closely.”
So, even though it was difficult at times personally, my years there were a huge leap forward for me and my research about cancer. Now we realize that older people get cancer in large part because they often have deteriorating immune systems, that they’re at a great risk of developing genetic mutations over time—that aging was a major prognostic factor for cancer. My time at NIA sowed the seeds of my work on aging and cancer, and then I joined The Wistar Institute, where that work flourished.