CONTENTS

1

Introduction

EVOLUTION IN THE FLESH

This is a book about cancer: its ancient origins, its modern manifestations, and its future fate. It is a book about where cancer came from, why it exists, and why it is so hard to cure.

This is also a book about a new way of looking at cancer—not as something that must be eliminated at all costs, but rather as something that must be controlled and shaped into a companion that we can live with.

Life has struggled with cancer since the dawn of multicellularity about two billion years ago. When we think of life on Earth, we typically think of multicellular organisms like animals and plants that are made up of more than one cell. The cells in a multicellular organism essentially divide the labor of making a living, cooperating, and coordinating to do all the functions that are needed in the body. On the other hand, unicellular life forms—like bacteria, yeasts, and protists—are made of a single cell that does all of the jobs of keeping that cell alive. Unicellular life dominated our planet for billions of years before multicellular life gained an evolutionary foothold. The world was cancer-free during these two billion years

when unicellular life reigned. But when multicellular life entered the scene, it ushered in a new player: cancer.

Cancer is a part of us, and it has been since our very beginnings as multicellular organisms. Remnants of cancers have been found in the skeletons of ancient humans, from Egyptian mummies to Central and South American hunter-gatherers. Cancer has been found in 1.7-million-year-old bones of our early human ancestors in "the cradle of humankind" in South Africa. Fossil evidence of cancer goes back further still; it is found in bones tens and even hundreds of millions of years old, from mammals, fish, and birds. Cancer goes back as far as the days when dinosaurs dominated life on our planet, and back even further than that, to a time when life was microscopically small. Cancer began before most of life as we know it even existed.

In order to manage cancer effectively, we must understand the evolutionary and ecological dynamics that underlie it. But we must also change our way of thinking about cancer, from viewing it as a temporary and tractable challenge to seeing it as a part of who we are as multicellular beings. Before multicellular life evolved, cancer did not exist because there were no bodies for cancer cells to proliferate inside of and ultimately invade. But once multicellular life emerged, cancer was able to emerge as well. Our very existence as multicellular organisms—as paragons of multicellular cooperation—is inextricably tied to our susceptibility to cancer.

In this book we will see how our bodies are made of cells that cooperate in myriad ways to make us functional multicellular organisms—for example, by controlling cell proliferation, distributing resources to cells that need them, and building complex organs and tissues. We will also see how cancer can evolve to exploit the cooperative cellular nature of our bodies: proliferating out of control, exploiting the resources in our bodies, and even turning our tissues into specialized niches for their own survival. In a word, cancer is cheating in the game that forms the most fundamental foundations of multicellular life.

A better understanding of the essential nature of cancer can help us to prevent and treat it more effectively, and also help us to see that

we are not alone in our struggles with cancer. All forms of multicellular life are affected by cancer. Our evolutionary relationship with cancer has shaped who we are. And if we want to truly understand what cancer is, we must understand how it evolved and how we evolved along with it.

We can look to the natural world to recognize what cancer is and how it evolves. One of the most beautiful examples is the crested cactus. Sometimes the cells in the growing tip of a cactus will mutate as a result of damage or infection. These mutations can disrupt the normal controls on cell proliferation during the growth of the plant. This often leads to striking formations: desert saguaros that look like they are wearing crowns, potted cacti that look like brains, garden cacti with knobby geometrical surfaces that evoke modern art (figure 1.1). Crested cacti are highly prized by professional botanists and backyard cactus lovers alike due to their beautiful and unusual mutated forms.

When I first saw a crested cactus on a visit to Arizona years ago, I was fascinated by the beauty and geometry of the plant. When I returned to my hotel room, I spent several hours looking at photographs of these natural biological formations and reading about them. I learned that the disrupted growth patterns of the mutated crested cacti sometimes result from damage during storms, sometimes from bacteria or viruses, and sometimes from genetic mutations during development.

I also learned that mutations that disrupt plant growth patterns are not unique to cacti—they happen across many plant species, from dandelions to pine trees. The technical term for these disrupted growth formations in plants is *fasciation*. Fasciated plants are often more delicate than their nonfasciated cousins, and sometimes they do not flower normally, making it harder for them to reproduce and propagate themselves—however, fasciated plants are often cared for and propagated by gardeners and botanists. With proper care, crested cacti and other fasciated plants can live for decades with these cancer-like formations.

Learning about crested cacti marked the beginning of my fascination with cancer across forms of life. I thought to myself at the

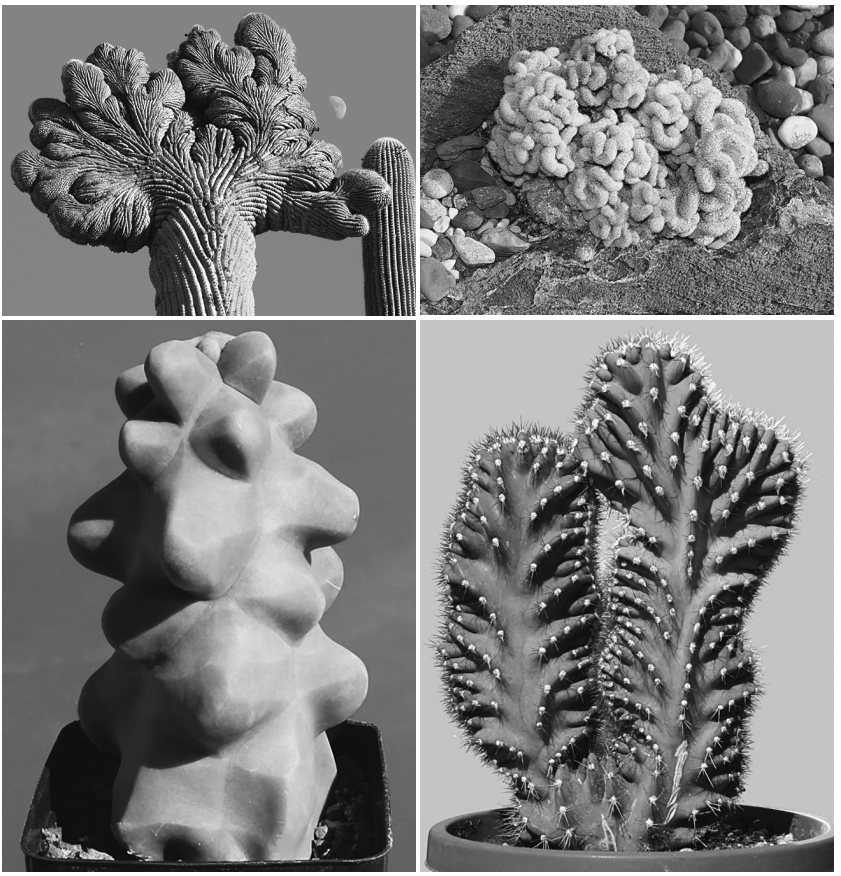

FIGURE 1.1 Cacti can develop abnormal growths as a result of disruption to the normal growth pattern. This can result in many beautiful and unique growth patterns that have similarities to cancer in animals. These cancer-like phenomena in plants, known as fasciations, can have negative effects on plant fitness including less flowering and greater susceptibility to injury or disease, but these plants also can survive with these cancer-like forms for decades if they have proper care. Images from left to right are a crested saguaro cactus, *Carnegiea gigantea*; a "brain cactus," *Mammillaria elongata cristata*; a "totem pole cactus," *Pachycereus schottii* f. *monstrosus*; and a *Cereus jamacaru* f. *cristatus*.

time: if we are going to understand cancer—what it is and why it can threaten our well-being and our lives—surely we need to know where cancer comes from, which means understanding the evolutionary origins of cancer across the tree of life. As I continued on my journey to understand the evolutionary origins of cancer, I discovered that cancer and cancer-like formations are ubiquitous across multicellular life. I found that cacti were not alone in having these cancer-like formations, but that there were also a myriad of other organisms that had cancer-like growths. I found pictures of mushrooms and coral and algae and insects with cancer-like growths. And I discovered that cancer was common across animals—from wild animals, to animals kept in zoos, to the domesticated animals that live with us in our own homes.

Why, I wondered, was cancer so pervasive across all forms of multicellular life? Cancer is uniquely a problem of multicellularity because multicellular life is made of many cells—cells that usually cooperate and regulate their behavior to make us functional organisms. Unicellular life forms don't get cancer because they are made of just one cell. This means that, for unicellular life, cell proliferation is the same as reproduction. But for multicellular life, too much cell proliferation can disrupt the normal development and structure of the multicellular organism.

You might feel like a unitary being, but in reality you are made of trillions of cells that are cooperating and coordinating their behavior every millisecond to make you a functional human being. The number of cells inside our bodies is mind-boggling—more than four thousand times the number of humans on Earth. We are thirty trillion cooperating, evolving, consuming, computing, gene-expressing, protein-producing cells. The body is literally a world unto itself. Each of these cells is like a little homunculus inside you, taking information from its environment, processing that information using complex genetic networks, and changing what it does in response to those inputs. Each cell has its own set of genes, unique gene expression (i.e., the specific proteins the cell is making) and its own physiology and behavior. The cooperation happening inside us is quite astounding. How can thirty trillion cells make a being that

seems so much like one single entity with one set of goals? How can I be made of so many cells yet feel so unitary?

One answer to these questions comes from evolutionary biology: We act and feel like unitary organisms because evolution has shaped us to be cooperative cellular societies. Perhaps we feel like unitary beings because evolution has fashioned us to act as though we are. We have been shaped by nearly one billion years of evolution on multicellular bodies to have cells that act in a way that enhances the survival and reproduction of the cooperative cellular society as a whole—the multicellular body. Our cells constrain their proliferation, divide labor, regulate their resource use, and even commit cell suicide for the benefit of the organism. The scope of cooperation inside us is beyond anything humans have ever accomplished—the cells inside us behave like a success story of a utopia, sharing resources, taking care of the shared environment, and regulating their behavior for the good of the body.

But sometimes this cellular cooperation breaks down. And when it does, this can set off an evolutionary and ecological process in the body that culminates in the ultimate form of cellular cheating: cancer. Cancer is what happens when cells stop cooperating and coordinating for the benefit of the multicellular body and start overusing resources, trashing the shared environment of the body, and replicating out of control. Inside the body, these cheating cells can have an evolutionary advantage over normal cells, despite the fact that they can damage the health and survival prospects of the body of which they are a part.

Although we feel like unitary individuals, fundamentally we are not. Evolution fashioned us to be incredibly functional as multicellular organisms, but we cannot escape the fact that we are a population of cells. Because we are made of a vast population of cells, evolution naturally occurs within our bodies. Cells in the body can evolve just as organisms in the natural world evolve. This is a very different way of thinking about who we are. In the traditional view, we are a unitary and relatively static "self." However, not only are we made of trillions of individual cells, we are made of trillions of cells that are part of a constantly evolving population. We are not

one entity, but rather many entities. And as we age, the population of cells that composes us continues to evolve, often in directions that put us at risk for cancer.

Cells are of course a part of who we are, yet they are also very much their own entities. Cells express genes, they process information, they behave—moving, consuming resources, and building extracellular structures like tissue architecture. In addition, they are a population inside our body that is evolving in a complex ecological environment. We need both of these perspectives—cells as a part of us and cells as their own unique evolving entities inside of us—to understand what cancer is and why we are vulnerable to it.

From the perspective of our bodies, cancer is a threat to our survival and well-being. From the perspective of the cell, cancer cells are only doing what every other living thing on this planet does: evolving in response to the ecological conditions they are in, sometimes in ways that are detrimental to the system of which they are a part. This leads to a seemingly paradoxical evolutionary scenario: Evolution favors bodies that are good at suppressing cancer, but evolution also favors cells inside the body that have the characteristics of cancer cells, such as rapid proliferation and high metabolism. How can both of these facts be true—on the one hand evolution favors cancer cells, while on the other hand evolution favors cancer suppression? As the narrative in this book unfolds, I will reveal how an evolutionary perspective can help us understand this apparent paradox.

The scale of cellular cooperation in our bodies is astonishing. But even more stunning is how resilient our bodies can be when faced with cellular cheating—how we can survive and thrive despite the threat of cancer. Multicellular bodies have evolved many different cancer suppression mechanisms over billions of years. These cancer suppression systems allow us to keep cellular cheating under control. Looking across species, we can also witness the diversity and power of these cancer suppression systems at work, and gain insights and inspiration for how we might better treat cancer in human beings. Like the crested cacti, which can coexist with their cancer-like growths for decades, perhaps we also can live with cancer.

Before I learned about cancer's evolutionary nature, I thought of cancer as nothing more than a rather uninteresting disease. My work focused on deep and fundamental questions about the evolution of life: Why are so many organisms social? What makes cooperation stable despite the possibility of exploitation from so-called cheaters? I had always been drawn to theoretical questions, so I shied away from any topic that seemed to require the memorization of an endless catalog of facts with no framework to hold them together. Cancer seemed to be one of those topics—no theoretical grounding, just an endless number of studies on mechanism after mechanism with no underlying principles to discover. It was certainly worthy of study because of its importance to human health, but I had no interest in studying it myself.

Then I moved to the University of Arizona to work as a postdoctoral researcher, and I began working with John Pepper, a pioneer in cancer evolution, a new field at the time. I realized that cancer was a cellular example of exactly what I was already studying: the challenges of maintaining cooperation in large-scale evolving systems in the face of cheaters.

My view of cancer started to change. I realized that cancer is a living entity evolving rapidly in the ecosystems of our bodies. It follows the same rules that all evolutionary and ecological systems follow. Placing cancer in an evolutionary framework provided a starting point for understanding its complexity.

The great evolutionary biologist Theodosius Dobzhansky—one of the pioneers of evolutionary thinking in the twentieth century—once said, "Nothing in biology makes sense except in the light of evolution." As I came to see cancer in this evolutionary light, I realized that cancer biology hadn't made sense to me before that point because I hadn't applied an evolutionary and ecological lens to understand it.

If Dobzhansky were around today, he might very well say, "Nothing in cancer biology makes sense except in the light of evolution." Evolution, ecology, and cooperation theory offer a starting point for understanding why cancer is such a complex, powerful, and dynamic force, and they can help us better understand who we are. And these

same tools can help us understand how cancer has shaped—and continues to shape—all of multicellular life.

Evolutionary theory explains how cancer can exist on two different levels. First, it shows how evolution among the cells in our body—often called somatic evolution—leads to cancer. Cancer is the literal embodiment of evolution: cells in our bodies are evolving inside us. The cells in our body vary in terms of how evolutionarily fit they are inside our bodies; some cells replicate faster and survive longer than others. The cells that proliferate more and survive longer subsequently make up a larger portion of the next generation and eventually come to dominate the population. This is evolution by natural selection, the same process that has shaped the evolution of organisms in the natural world.

In addition, evolutionary theory helps explain why cancer has persisted over the course of life on Earth. Organisms have evolved over millions of years to suppress cancer—to keep somatic evolution under control—so that we can live long and evolutionarily successful lives. These cancer suppression systems are the reason that multicellular life is even possible—without them, multicellularity would never have been able to overcome the challenges of cellular cheating from within. But these cancer suppression systems are not perfect. Evolutionarily speaking, keeping would-be cancer cells 100 percent under control is not possible.

The reasons we can't completely suppress cancer are varied, and each is fascinating in its own right. For example, one reason why organisms don't evolve to suppress cancer completely is because of trade-offs with other traits that affect the fitness of the organism, like fertility. Sometimes, lower cancer risk is associated with lower fertility, creating an evolutionary bind for organisms evolving to suppress cancer. In addition, organisms can't suppress cancer completely because there is a mismatch between past and current environments: modern humans are exposed to mutagens like cigarette smoke and lifestyle factors such as low physical activity, which lead to greater susceptibility to cancer. An even more bizarre reason why we can't suppress cancer is that there is a battle over our growth happening between genes we inherit from our mothers and genes

we inherit from our fathers. Some of the genes we inherited from our fathers are epigenetically set to promote growth and cell proliferation, contributing to an increased risk of cancer. Cancer exists because of the tension between two evolutionary processes acting on two different scales: cells evolve in the body via somatic evolution, and bodies can't evolve to completely suppress this process of somatic evolution.

The environment that cancer cells occupy in the body can greatly affect whether would-be cancer cells die or survive and thrive. In cancer biology, the environment around a tumor is called the tumor microenvironment. This is essentially the ecosystem of the tumor, in many ways like an ecosystem in the natural world. The ecosystem of the tumor provides necessary resources that allow the cells in the tumor to survive and thrive, but it can also threaten the survival of cells when resources run out, waste products build up, and the immune system starts preying on cancer cells. Cancer cells can alter their environment as they consume resources such as glucose; for instance, they can reduce the supply of resources for neighboring cells and leave behind waste products like acid. Those changes, however, can trash the ecology of the cancer cells, making it difficult for them to survive and thrive. The destruction of the microenvironment can create selection pressures for those cells to move. Cells that can move and are able to relocate to a new and better environment in the body will survive and leave more cellular progeny, spurring the evolution of invasive and metastatic cells. Ecology is central to the ways in which cancer emerges and progresses. Just as we can't understand how and why organisms evolve without knowing about their environments, we can't understand how and why cancer evolves without knowing the ecological dynamics in and around a cancerous tumor.

The common metaphor for cancer is war—patients "fight," "battle," "win," or "lose." The war metaphor for cancer is powerful and compelling. It can help to rally support for cancer research and bring people together around a common goal, but it can also be misleading. We can't completely eradicate something that is fundamentally a part of us. This aggressive approach to the disease seems like a good idea if we view cancer as an enemy to eradicate. But unless

we see cancer for what it is—a population of diverse cells evolving in response to every treatment we throw at it—we run the risk of discounting or outright dismissing less aggressive forms of treatment.

The war metaphor encourages an aggressive outlook that can lead to other consequences as well. When we treat cancer with high-dose therapies, this can give an evolutionary advantage to cells that are resistant to those therapies, making our treatments less effective for long-term tumor control. For terminal cancers, attacking with the highest-dose therapies is often not the ideal strategy. Approaching cancer with an aggressive mind-set can also have a negative effect on prevention. When people are presented with a war metaphor for cancer, they report being less likely to engage in some cancer-prevention behaviors, like stopping smoking. In addition, aggressive language related to treatment can increase stress levels for cancer patients and their families.

Cancer is not an enemy in the typical sense of the term. Cancer is not an organized and homogenous army that is collectively set on our destruction. Instead, it is a disorganized and heterogenous population of cells that is dynamically responding to our treatments. When we fight cancer, we are fighting against an inevitable process: the process of evolution. We can slow down that process or change its course, but we can't make the process stop.

Cancer is the literal embodiment of evolution. It is evolution in the flesh. We are susceptible to cancer because we are made of a population of cells that evolves over our lifetimes. Cancer will be here for as long as multicellular life endures on our planet. The sooner we can accept that, the sooner we can use our knowledge to effectively keep cancer under control.

We can't win a war against a process of evolution, a process of ecological change in our bodies, a process of cellular free-riding taking over multicellular cooperation. But we can shape that process so it is less harmful to us. We can gain insights and strategies to help us shape cancer into something more benign and less threatening—in other words, something we can live with.

Fighting a war on cancer for which the only acceptable outcome is complete destruction of the enemy, as opposed to using

circumscribed strategies to exploit cancer's vulnerabilities, is much like the contrasting war strategies of two Greek gods of war, Athena and Ares. I grew up in a largely Greek household, living first in Athens and then in the suburbs of Chicago, and Greek mythology was an important part of my childhood. I was raised in part by my grandmother, Athena (after whom I was named). Of course, I had an interest in understanding my namesake. Athena is the goddess of wisdom and war, but not just any kind of war; she is the goddess of strategy. Rather than winning by brute force, Athena wins by understanding the goals and vulnerabilities of the enemy and then exploiting those to achieve victory with minimum force and without unnecessary collateral damage. Ares, on the other hand, approaches battle with maximum aggression and with the goal of inflicting as much damage as possible on the enemy at all costs.

Which approach is right for cancer? Should we fight by brute force like Ares, or should we plan a strategy (like Athena would do) that exploits the vulnerabilities of our adversary? From what we know about cancer, it is clear that Athena's approach is more likely to extend the lives of cancer patients, improving their quality of life as well. (And I'm not just saying that because I'm named after her.)

Cancer is an inexorable part of our lives and histories as individuals, and as multicellular organisms. In this book, I will use our evolutionary history as the basis for discovering insights into what cancer is, why it emerges, and how we can better treat it. I will argue that cancer is more than just a disease; it is a window into the origins of life, the challenges of large-scale cooperation, the nature of multicellularity, and the process of evolution itself.

INDEX

Note: Page numbers in *italics* indicate figures.