TPWKY - EP 203 - Cancer 2

EW: [00:00:00] Throughout this series, we'll be discussing many aspects of cancer diagnosis and treatment, and we will be sharing several personal stories related to cancer. Some listeners might find this content upsetting. Please listen with discretion.

Firsthand 1: In the fall of 2024, I had just sent my oldest off to start his freshman year of college, and my youngest was starting high school. We had a very busy summer and I was trying to settle into our new normal. I'd started to gain weight earlier in the year, and even more recently had started becoming very fatigued. When I talked to my gynecologist about it at my checkup, we discussed that I was probably beginning perimenopause. Most of my symptoms seemed to line up. However, in late September on a Sunday afternoon, I got a horrible stomach ache. After eating lunch, the stomach ache persisted off and on for a few days and I thought maybe I'd had food poisoning. It eventually got somewhat better, but I was still sore and even made the comment to my coworkers that I felt like I had done a million crunches. I started to have cramping again one week later, again on a Sunday, but this time I was also having chills and nausea, so I went to an urgent care clinic where they did an x-ray and said that I was constipated. However, they wanted me to follow up with my PCP. The next morning I was unable to see my PCP, but I did see an on-call provider and she sent me for a CT scan. Thankfully, I was able to get it done that day.

On my way home from the CT scan, the on-call provider called me and told me to turn around and go to the emergency room as soon as possible. Her exact words were, your skin looks rough. I was septic and had emergency surgery the next day for a perforated bowel, and they also removed a suspicious part of my colon. It came back as stage two colon cancer. Genetic testing revealed that I had Lynch syndrome, which is a genetic condition that increases one's odds for gi, colorectal, ovarian, uterine, and other types of cancers. I also tested positive for PT one tumor predisposition syndrome. Because of these markers and the fact that my grandmother passed from ovarian cancer, I chose to have a complete hysterectomy, including ovaries. I also have to have yearly colonoscopies and egs and other monitoring that needs to be done, including skin checks every six months, regular CT scans and lab work. I feel very thankful to be NED or no evidence of disease at just shy of 15 months, but I've made it my mission to inform and encourage my friends and family members to get their colonoscopy. I was 45 at the time of diagnosis and was able to start my screening that year. But I kept putting it off because I was too busy. And if I'm completely honest, I didn't think anything like this would happen to me. I

considered myself relatively healthy. I ate right. I exercised, but my genetics had other ideas.

Firsthand 2: Story began in the fall of 2024 with the weirdest diagnosis I could have never imagined for myself. And I've imagined tons of diagnoses. I'm a nurse and a Virgo and an oldest child who grew up in the eighties and nineties who copes by catastrophizing. So trust me, I've diagnosed myself with plenty of things over the years, but not metastatic breast cancer of all the things that was not on my lifetime bingo card. Among the many things that breast cancer has forced me to change, it was that I have to be okay with vulnerability and frailty. I've never been comfortable with those things before. My body has really been through the ringer this past year, from surgery to chemo, to radiation. Now oral chemo. It has been poked, prodded, scanned, chopped up, stabbed, poisoned, and irradiated. I should have known what was in store for us when I was getting my implanted chemo port and they had to tape my breasts to the side rail so that it wouldn't move and mess up the procedure. That was just the beginning. I have literally lost track of the number of people who have seen my breasts, the number of imaging procedures or scans I've had done.

I've never felt worse in my life than I have this past year and I went to nursing school. There have been times I wanted to die just to let the cancer take me. My body betrayed me, and not just by trying to kill me, it also made it so I had no control over things. So my bowel or my bladder, I crapped in my pants when I thought it was just gas or like that time when I peed on the sidewalk while walking. My dogs super fun. Even now, my chemo brain is legit and I don't remember what it's like to not be nauseated. I've had to learn that I don't have to put a brave face on. I can be vulnerable. I can ask for help and I can share when my instinct really has always been to protect others from the ugliness that I've been facing. It doesn't diminish who I am as a caregiver. It really is okay to prioritize myself and my needs that I can take time to listen to my body, and I can pause and I can rest. I have literally been fighting for my life and it's okay to take a day off. Thanks Cancer for these epic life lessons. I'm better at advocating for myself now and listening to my body and its needs. It is [00:05:00] okay to give myself grace. I do have to say though, I would give breast cancer zero stars. I do not recommend it.

EW: Thank you everyone who has shared your story with us. And also just a big thank you to everyone who wrote in to share your story. It is e Every time I just pinch myself and I'm so grateful that so many of you are willing to share these vulnerable experiences. Yeah. And because this is really, is like these firsthand accounts are the backbone of this, of this podcast. They bring so much that we couldn't, that we could not,

EAU: yeah, they absolutely do. This podcast would not be the same without your firsthand account. So thank you. Yeah. So much. And we have a lot more that we'll be sharing with you throughout this episode and throughout this series as well. So thank you again to everyone who submitted, um, your firsthand account. We really wish that we could have included every single story that we had the privilege to hear. Yeah. So thank you. It means a lot to us.

EW: It does. Hi, I'm Erin Welsh.

EAU: And I'm Erin Allmann Updyke.

EW: And this is, This Podcast Will Kill You.

EAU: Welcome to episode two of our series on Cancer,

EW: cancer. It's a big one.

EAU: It really is.

EW: Uh, if this is your first time tuning in mm-hmm. To this series, go check out the first episode. Yeah. We've got four total common for you. And, um, and each of these episodes covers a different aspect of cancer. Right. And really our intent with this is just to lay the foundations of knowledge so that in the future we'll be able to, then you'll be able to like, oh yeah. I know what cancer is, right? Because in this episode on lung cancer, because I listened to the cancer series.

EAU: Exactly, exactly, exactly.

EW: Yeah. It gives us an opportunity to explore the big picture mm-hmm. Of what this all means.

EAU: Right.

EW: What does that mean? How are these episodes organized? Great question. We'd

EAU: love to tell you,

EW: if you didn't listen last week. Last week we really explored the concept of cancer from both like a biological perspective, well, more clinical perspective,

as well as like through history, how that has changed and our current conception of it. Uh, in this episode, we're gonna be going over the evolutionary aspects of cancer, the cellular aspects of cancer, like why is cancer so prevalent? Right? Next episode, treatment.

EAU: Mm-hmm.

EW: That's that episode. Yeah. I mean that encompasses a lot.

EAU: Yeah.

EW: And the last episode, the fourth and final, is all about, um, screening, prevention, kind of understanding the landscape of cancer today and where we might go from here.

EAU: Exactly, exactly.

EW: Yeah.

EAU: And that's all quite a lot of ground Yes. To cover, but there's a lot that is going to be unexplored. And like you said, Erin, this is really the jumping off point. These are not the only cancer episodes that we are ever going to do. We have lots of plans to cover so many individual types of cancers and. We also have a massive list of sources. If anyone gets inspired and wants to learn more about cancer from a big picture perspective or individual cancers, my goodness, do we have sources for you?

EW: So many opportunities to do that? So, yeah. Yeah. Uh, and as you'll hear, no two cancers or experiences with cancer are exactly alike. And so again, we are just so grateful to the providers of our firsthand accounts to really just showed us like a sample Yeah. Of what it means to have cancer, to be diagnosed with cancer, to be going through treatment, to lose someone, to cancer, to be a caregiver. Just so many different facets of this experience that to fix

EAU: so much of our lives.

EW: Yeah. That, you know, we're in these episodes, we're really talking about the biology of mm-hmm. Like we're talking about from a biological and historical perspectives. Right. We're not talking about these experiences. And so that is where these firsthand accounts have been so integral. Yeah. So thank you again.

EAU: Yeah. Thank you. Thank you. They really do mean everything to us.

EW: Yeah.

EAU: So,

EW: okay. One more piece of business.

EAU: Last piece of business.

EW: Quarantini time. We're still doing it.

EAU: We're still doing it. If you didn't hear last week, uh, we are no longer doing alcohol in our quarantining recipes, so you could consider them all placebo burritos, but we're gonna call 'em quarantining. That's just

EW: whatever strikes

EAU: us. And this week we're drinking

EW: the crab.

EAU: The crab.

EW: It's an affogato

EAU: espresso ice cream. Let's go get one after this.

EW: Subscribe to our socials to, yeah, let's go get one. Subscribe to our socials to, uh, see how it's made. Mm-hmm. And, um, check out our website where you can find all their other sorts of T-P-W-K-Y [00:10:00] related things. Mm-hmm.

EAU: This podcast will kill you.com.

EW: Yeah, check it

EAU: out. Thank you. Rate, review, and subscribe. We're also on YouTube

EW: and

EAU: now, and

EW: now for the real stuff.

EAU: The real stuff. Okay. Let us get into the biology of cancer. Shall we?

EW: We shall after this short break.

Firsthand 3: On August 28th, 2025, I got a call from my dermatologist. He told me a biopsy on what I thought were hives, had come back as malt lymphoma and asked me to come into his office so we could talk. What followed were months of emotional whiplash. At first, I didn't understand the diagnosis. Then came long stretches of waiting, waiting to learn what my next steps were, waiting for answers, and finally getting information without a clear plan. Eventually, a treatment plan came together, but the uncertainty leading up to it was one of the hardest parts. Malt Lymphoma stands for mucosa associated Lymphoid tissue lymphoma. It's a slow growing form of non-Hodgkin's lymphoma, and in my case, it appeared in my skin. I was told there are a few possible causes including infections and genetics, but for me, the most likely explanation was simply bad luck. This type of lymphoma is considered rare and is more commonly found in men in their fifties and sixties. I was 31 active teaching and competing in country dance and otherwise healthy, which made the diagnosis feel especially surreal. After consulting, both my local oncologist and an oncologist at the Mayo Clinic, my husband and I decided on localized immunotherapy rather than surgery and radiation.

I traveled to the Mayo Clinic in Scottsdale, Arizona for treatment with rituximab, which involved injecting the medication directly into the tumors. At the time, I had nine tumors across my arms. The process involved numbing injections followed by the drug itself, totaling about 20 to 30 injections per session. I have a high pain tolerance, but right after treatment, my body started shaking and I felt extremely cold. It lasted about five minutes, and then I was fine, but it was still unsettling. I remember looking at my husband and saying, I wasn't sure I could do it again. I did. After three sessions, the tumors began to shrink. Six weeks after my last treatment, they have almost completely disappeared. Now I continue regular monitoring. Any new bumps are considered a recurrence and something I may live with long term. While I'm grateful for an overall favorable prognosis, the experience permanently changed how I think about my health and my relationship with my body.

Firsthand 4: When I was 32 in 2016, I was diagnosed with breast cancer. I found a lump in the shower. Went to my local doctor and within 10 days I had been diagnosed. What followed was just a whirlwind. I had a right-sided mastectomy and full node clearance. I had an immediate DAP reconstruction

where they took the fat from my stomach and uh, made a new breast out of it. I had egg retrieval because we hadn't had children, and then I had six rounds of chemotherapy and radiation for three weeks. In 20 25, 9 years later, I'd had a sore hip, and it was starting to affect my day-to-day life. So I went to the doctor, I saw the physio who wasn't worried about it, went home, went on a trip where it felt like something had moved and I assumed I'd slipped a disc. So I came back, went to the physio again, a female physio this time, and she referred me immediately. When I saw the physio at the hospital, again, he wasn't too worried. I didn't have any massive red flags, but he sent me for an MRI, just to make sure, because I had a history of cancer. And at the end of March, I got a phone call to say that unfortunately I had several deposits in my spine and in both hips, and it looked like secondary breast cancer. I had to have a bone biopsy while I was awake, which I do not recommend. Um, and I found out that, yeah, it definitely was cancer and I would have to be treated at this point. I had no idea what that meant. I didn't know if it had spread. I didn't know if I had weeks or days or months left to live. And it just, uh, it just absolutely, it was horrendous.

That was nine months ago. I am medicated. I'm on a treatment called Ribociclib, which is a tablet, so I take it almost every day. It's really non-invasive, and I'm now at the point where I only have to go into the hospital every two or three months. I hope that I continue to improve or stay stable, which is what my last couple of scans have showed. [00:15:00] I know some people have been on this drug for eight to 10 years and are just still going, so I really hope that I continue to live and thrive like I am doing now for a long time to come.

EAU: So I actually wanna start this week's episode exactly where I started last week's episode. Not where I ended it.

EW: Okay.

EAU: But where I started it, which is with the definition of cancer.

EW: Okay.

EAU: Which is a logical blaze to start.

EW: Yeah, yeah, yeah. It feels

EAU: like.

EW: Yeah, sure.

EAU: So I'll go back to that. National Cancer Institute definition.

EW: Great

EAU: quote. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. So what does that really mean? If you've ever built a Lego kit, you've built a Lego kit at some point in your life,

EW: I've built Legos. Okay.

EAU: Yeah,

EW: but I don't know if I ever had a kit.

EAU: Okay. So, uh, if you have ever built, if anyone listening and watching has built a Lego kit, you could imagine that it comes with a set of instructions. Like if you wanna build a rocket ship that really looks like a rocket ship, you're gonna need to follow this specific instructions that come in that Lego box.

EW: I mean, I've built many Ikea pieces of furniture very

EAU: similar. Is

EW: that the same kind of thing? Similar. Okay, great, great,

EAU: great. Very similar idea, just more pieces, et cetera. Perfect. But in the box there are also a lot of different kinds of pieces of Legos or IKEA bits, right? Some of them all look the same. There's like 15 different dowels. There's like 24 different four by four squares or whatever. Oh gosh.

EW: Yeah.

EAU: And some of them look a little bit different from each other. And in order to build the thing you are trying to build, you have to follow those instructions really explicitly.

EW: I kind of, I, I have to admit, I love putting together, I see a furniture,

EAU: you would love a Lego kit then

EW: I'm sure that I would.

EAU: Um, our bodies. Are kind of the same. We have to function as one entire organism, a rocket ship, an IKEA piece of furniture, if you will. But we are made up of trillions of individual cells, and we started out as just one cell, which is a little bit different than IKEA furniture because our cell had to divide and divide a bunch of times. But this process of cell division is extremely tightly regulated.

EW: Oh, yeah.

EAU: Because if every cell in our body just divided nonstop, it would be madness.

EW: It would be a problem

EAU: would be we wouldn't be here. In short.

EW: Yeah.

EAU: So we have sets of instructions that are encoded into our DNA, which have patterns, instructions that our cells are going to use to make the right types of tissue in the right types of places.

EW: Mm-hmm.

EAU: To grow and to replicate when it's appropriate to grow and replicate and to not like. Build a castle on top of your rocket ship out of all of your Lego bricks. Right,

EW: right. It's like instructions on instructions. On instructions. Exactly. You'll grow and replicate, but not only that, you're gonna become this specific type of cell, this specific type of, this specific type of organ in this specific little bit,

EAU: and then you're gonna forget how to do all those other things that you used to be able to do. Yeah, we'll get there. So our cells determine when and how to divide based on a lot of different sets of instructions, and there is redundancy built into this process, and that is to protect against the inevitable mistakes that occur. In the process of cell replication. Mm-hmm. So we have a lot of checkpoints in what is called our cell cycle and how our cells divide. Our cells rely on signals and communication with other cells. And like you mentioned, cells also differentiate, so they specialize into different types of cells

in order to organize into tissues and organs. And then they only do that one certain thing. Your heart cell is just heart selling. It's not out here trying to be a skin cell anymore.

EW: No.

EAU: Even though they came from the same place.

EW: Right.

EAU: Okay. So cancer cells kind of take all of the pieces out of a Lego box, throw out the instruction manual, ignore any guidance on what these rules of building are supposed to be.

EW: Mm-hmm.

EAU: So to really understand how this is happening, we can look through some of the rules of cell growth in detail and see how cancer cells are just breaking every single one of. And, and I know you're gonna get into this a little bit more, Erin, they also leverage these rules. Yeah. They, they do in a way that benefits them and not us.

EW: Mm-hmm.

EAU: So excited about this. So one of the rules that [00:20:00] ourselves typically follow is that they only grow and divide in the presence of what are called growth factors or growth signals. Mm-hmm. Meaning that they're waiting for signals from cells and around them to determine if it is actually the right time to divide. Right. Cancer cells either ignore these signals entirely, or they just make their own. They just make their own growth signal and then they're like, Hey, we're, we're telling you to grow, keep growing.

EW: Mm-hmm. Mm-hmm.

EAU: So what we see, and you talked about this in last week's episode, Erin, in a lot of cancers are what are called oncogene mutations. Yes. And this means changes in certain genes that are involved in turning on. Growth, replication and development signals all the time, which allows for this continuous cell division and growth of these masses of cells. So we see mutations in oncogenes in a lot of cancers. Almost all cancers have at least some oncogene mutations. Right. And there are a few that are quite prevalent, like a few big ones that are

prevalent in nearly all cancers. Yep. So you might have heard of some of these when you're looking up cancer things, some of these are like RAs or RAS.

EW: Yep.

EAU: And there's a bunch of different versions of RAs. And these are things that basically when they are switched on, they just allow for cells to continue to grow uncontrollably. Right. And they're switched on in a lot of cancers.

EW: Gas pedal to the floor,

EAU: gas pedal to the floor. Another mechanism that you also talked about a little bit last week's episode is that. All of our cells typically have the ability to turn off cell division if they need to turn it off entirely. And they're able to recognize if our cells and the DNA within our cells gets damaged mm-hmm. So that they can stop that process of cell division if there's damaged cells or damaged DNA and not replicate that damaged DNA. Yep. One of the ways that we do this in, in our cells, typically is through a process called apoptosis. Which is programmed cell death. And it basically is that our cells are recognizing damage and they're saying, this cell, you need to die this cell. You need to die.

EW: Right.

EAU: Stop

EW: done

EAU: destruct. Exactly. And then our immune system comes in and they do the thing.

EW: Mm-hmm. They do the job. Mm-hmm. Mm-hmm.

EAU: Cancer cells, you can guess turn these mechanisms off.

EW: Yep.

EAU: And a lot of the genes involved in this process, we call tumor suppressor genes.

EW: Right.

EAU: And in cancer, these mechanisms are turned off.

EW: Yep.

EAU: That's the get take out. The break of the car, the

EW: break is broken,

EAU: it's completely gone. Yeah. And there are a lot of different kinds of tumor suppressor genes. But I'm gonna give everyone a concrete example 'cause then I think we'll be able to connect it back.

EW: Yeah.

EAU: It's BRCA.

EW: Oh, okay.

EAU: Okay.

EW: Okay.

EAU: You gave me a face, like it was gonna be something different. I

EW: don't know.

EAU: It will be something different. The face that you're making.

EW: Yes,

EAU: yes, yes. Um, yeah. But BRCA one and BRCA two, I think most of us has probably heard of these are the genetic mutations that are associated with a significantly increased risk of breast cancer, ovarian cancer, but also melanomas, pancreatic cancer, lots of different types of cancers. And these are tumor suppressor genes. So if somebody is born with a certain version of these genes, the certain copy of BRCA one or BRCA two, then they are not making a protein. And in this case, the protein is supposed to help identify and repair broken DNA. So if you can't do this, if you can't identify and repair broken DNA, then your cells have a tendency to accumulate more mutations. Mm-hmm. And that leads to this increased risk of cancer. But there is another classic

tumor suppressor that I feel obligated to talk about because it is. Its function is affected in almost every case of cancer, and that is TP 53.

EW: That's what I thought you were gonna talk about.

EAU: Yeah, that's what I figured.

EW: What, what proportion of cancers?

EAU: Well, okay, 50% of cancers have a mutation in this specific gene. TP 53.

EW: Yes.

EAU: But almost all cancers over 90% have some kind of malfunction of the function of this P 53 protein. So this TP 53 gene encodes for a bunch of different versions of this specific protein that does. So many different things in our cell cycle. It activates DNA repair proteins. It halts the cell cycle. If there is damage to DNA, it initiates apoptosis. It's involved in a process called senescence, which is very important in cancer biology and is like when our cells age to a point where our body decides stop replicating forever.

EW: Right. You're too hard to keep an eye on.

EAU: Exactly. It's enough. Yeah. You're unreliable at this point. I'm taking away the keys. Yes. You know? Yes. Um, and we see mutations in this particular gene, like I said, in half of all human cancers and disruption of the function. So even if the gene is still making the protein

EW: somewhere, yeah.

EAU: Something else, the protein can't do its job anymore. Mm-hmm. Mm-hmm. So this particular gene is really important in cancer formation.

EW: It's a big deal.

EAU: It's a really big deal. There's a condition where people could be born with a non-functional copy [00:25:00] of this gene and that results in a condition called Lee Fra Manini Syndrome.

EW: Next week's book, book club episode.

EAU: Oh, amazing.

EW: Yes.

EAU: Oh, so definitely listen to that one. Mm-hmm. Um, and that you are prone to a wide variety of, of cancers with Lee from Manini Syndrome. Mm-hmm. And usually quite early in life compared to when we typically see cancers.

EW: Mm-hmm.

EAU: But there's more. There's more that cancer cells do. Cancer cells also, they start to upregulate. So like encourage this process that keeps them alive indefinitely. So most of our other cells can only divide a certain number of times.

EW: Mm-hmm.

EAU: Uh, and then at a certain point, they start making mistakes that are completely deleterious to the cell. Right. So then they just can't do it. Cancer cells have enzymes that they make to keep our DNA viable to continue replicating forever.

EW: Right. Override, override, override.

EAU: Override switch. Override switch. Mm-hmm. We also see that cancer cells alter how they do metabolism.

EW: Yeah. They do.

EAU: They alter how they do metabolism in ways that allow them to survive better. For example, they can survive better in low oxygen environments.

EW: Mm-hmm.

EAU: They can adapt to whatever nutrients are available in the environment. And speaking of oxygen, because oxygen is really important for all of our cells to be able to grow, and the way that our cells get oxygen in our bodies is through our bloodstream,

EW: of course.

EAU: And to get blood, you need blood vessels because that's where our blood happens to be contained. So cancerous tumors upregulate the process of angiogenesis, which is the formation of blood vessels. So they make their own blood vessels in order to feed themselves. Yep. We also see changes like modifications of the genome that aren't just mutations, other ways that they change the genome without having to have an actual DNA mutation in there, we see that they can also, we said how cells have to differentiate and become like only a heart cell. Yeah. Cancer cells can undo that differentiation to make cells look more like stem cells.

EW: Mm-hmm.

EAU: Which divide indefinitely and can do any sorts of function, et cetera.

EW: We can, yeah, we can do whatever, take whatever form

EAU: right. Exactly. So that's like on the tiniest little micro level. Yeah. All of our cells are doing this really weird and wacky stuff on the slightly more macro level, looking a little bit bigger at like the cancers and their environment.

EW: Mm-hmm. If we will. Mm-hmm. The ecology of a tumor.

EAU: Ecology of a tumor, they have really big impacts on things like our inflammatory system.

EW: Yeah.

EAU: And what's so interesting is that cancers activate our inflammatory system. They activate our immune system and pathways across basically all cancers, and yet they also are. Incredibly good at avoiding our immune system's destructive processes. Yeah. So they are using the parts that benefit them, like because inflammation brings oxygen, it brings blood, it brings other cells and things like that. But then they are still evading the destructive process, our immune system that would normally get rid of them. And of course, like I mentioned last week, one of the biggest things that cancerous tumors do, or that cancer cells do in general is that they are traveling. They are traveling widely throughout our body. Individual cells, clumps of cells are breaking off and they are traveling throughout our body, which can then cause additional disease in distant areas. So cancer cells do a lot.

EW: Mm-hmm.

EAU: And a lot of these changes are due to mutations in our DNA that are allowing for some of this evasion of typical checkpoints, like the continued replication and things like that. But we also can see a lot of these types of mutations in people that will never develop cancer. Yeah. And in a lot of our nor so-called normal cells, like the same mutations can be present, but there's no cancer there. And that is why cancer is not just a genetic disease. It's a disease of what we call G by E or genetic and environmental interactions.

EW: Right.

EAU: So the mutations that we know are associated with cancer are a necessary. Not sufficient part of cancer biology.

EW: Right. A cancerous cell doesn't turn cancer simply because it has one mutation.

EAU: Exactly. Exactly. These mutations can arise spontaneously. We might be born with some of them, but they also could arise from exposures. Mm-hmm. To things that are actually mutagens. And that might be like tobacco smoke, which has so many different carcinogens in it that do in fact cause damage to our DNA and can result in some of these deleterious changes. Or like a virus, like you talked about last week, inserting some of these oncogenes into our DNA.

EW: Mm-hmm.

EAU: But there also has to be something that stimulates these [00:30:00] type of mutations to actually persist and take over. So. We now know, and we don't fully understand this all, Erin, but that some of especially the environmental exposures might contribute in more ways than just affecting our DNA.

EW: Mm-hmm.

EAU: Right? So like, yes, tobacco smoke is going to damage your DNA and inhibit DNA repair and increase your mutation burden, but a lot of exposures also are going to potentially just create an environment in our cells and in our tissue, whether that's increase in inflammation,

EW: right?

EAU: Whether that's whatever it is that we don't fully understand this like tumor microenvironment effect, but we know that it's an essential part of this

cancer formation process. And that's where we think that a lot of these environmental exposures that we don't fully understand the direct links. How those might be playing a role.

EW: Right. Like mechanistically, it's not just about the genetic changes, it's also about these other things that allow for that cell to evade immune versus detection or to uh, get nutrients or whatever. Exactly, exactly. Like all these different factors.

EAU: Exactly.

EW: Yeah.

EAU: And I feel like what this really underscores is how much of a kind of perfect storm of events has to happen for cancers to be able to develop. And it also helps us know why aging is such an important risk factor because the more that your cells divide, the more likely any of these mutations might take place.

EW: Mm-hmm.

EAU: But you really do have to have the right sets of mutations. Right cells in the right environment with the right supporting cell cast at the right time for these cancer cells to be able to take hold and eventually take over.

EW: It is, it's a perfect storm, but it's storming all the time.

EAU: It's storming all the time. Right. And while all cancers break, all of these different rules mm-hmm. That I went over, every single one does it in slightly different ways.

EW: Right. The pathway is different.

EAU: Different,

EW: the progression is different, the mutations might be different. That, you know, nutrient what whatever, everything is

EAU: different. Exactly. Every individual exposure that you've had, your particular DNA and how it's interacting with those exposures. And that is why it makes it really hard to generalize our treatments for cancer. Even if we're like,

but this is the same receptor, or this is the same mutation, this is the same protein. Yeah. Why isn't this treatment working exactly the same?

EW: Yep.

EAU: Right. So really cancer is, I'm really wanting you to start talking Erin, because cancer is kind of our cells forgetting how to function as a multicellular organism. Yeah. It's our cells all of a sudden, but not all of a sudden, 'cause it's a long process, but starting to live as parasites as these like unicellular organisms that no longer abide by all of the rules that makes them good neighbors to all of the other cells around them.

EW: But they also do cooperate within a tumor.

EAU: Ooh, I can't wait for you to tell me all about that, Erin. And they do and they cooperate. Mm-hmm. With that particular environment.

EW: Right.

EAU: And they make it very conducive for themselves. Yeah. And themselves only. And they're leveraging our body systems in order to do this. Mm-hmm. So Erin, I'm hoping that you can shed some light on. The evolution of cancers and why it is that we are so susceptible to these.

EW: It's so funny that you said shed some light. 'cause I literally say something just like that. I

EAU: can't wait.

Firsthand 5: Hey, my name is Kendra and I am 33. I was diagnosed with stage three C ovarian cancer in 2024. My diagnosis came as a surprise, as I didn't have any signs or symptoms to think that I needed to be seen for anything. I was just going in to get my IUD replaced and needed an ultrasound, and then they found the ovarian cancer. Sadly, ovarian cancer doesn't have a lot of noticeable signs or symptoms and so. It was a fluke that it was found after being sent to gynecology oncology to figure out a treatment plan. I was sent off for some genetic testing where I found I was also BRCA one positive with the BRCA gene. I have an increased risk of cancers such as breast, ovarian cancer, as well as pancreatic cancer and some other cancers. Along with getting myself genetically tested. My doctor also sent my cancer off to be genetically tested, where they were able to find a few different treatment plans that would be helpful, that were specifically targeted towards my type of cancer. This has been

an [00:35:00] overwhelming and scary process, and I have learned so much about the medical research that has been done and the advancements that we've made looking at genetics and how Im impacts people's risks for cancer.

Firsthand 6: Hi, my name is Michelle. I'm 42 years old and I live on Long Island, New York. My husband Ed was diagnosed with glioblastoma, which is the most aggressive form of brain cancer in July of 2024 and passed away in October of 2025 at 44 years old. We are the parents of a teenage son, and Ed was a talented radio producer. So speaking about his experience on a podcast is actually something that really connects to who he was in his professional life. Ed had a sinus infection and then for two weeks following, had intermittent pressure headaches. Urgent care said it's probably a lingering sinus infection, and he went to his primary care doctor who said, let's get an MRI, just in case, because why take the chance? So scheduled an MRI. A couple of days before the MRI, he came to me and said, this isn't getting any better. And I said, why don't you just go to the ER just for peace of mind. I actually Googled whether or not a headache was a good reason to go to the er. And he drove himself and said, don't cancel our dinner plans. And three hours later he called me and said, you need to get here now. They found something on the CAT scan and thankfully we only live five minutes from the hospital. It was an incredibly traumatic 14 and a half months. And when I say this was the shock of our lives, it's a tremendous understatement.

There's so much I could discuss about our experience, but one thing that stands out is that glioblastoma is not common at our age. So it was so isolating going through this and him seeing that he was the youngest person in the waiting room every single time when he was looking for support groups for himself, it was mostly people who were 20 to 30 years older. When I was looking for caregiver support groups, it was mostly children taking care of parents or retired couples and. We were like, where are all the people who are working full-time, who had to put their careers on hold, who have to care full-time, while also making sure their school aged children's routines are intact and have extracurricular activities to take their kids to. The worst was when people would see us and say, you're too young to be dealing with this, and I'm trying to navigate that as a widow right now. Apparently the universe didn't get the memo that we're too young to be dealing with this.

EW: We learned last week that cancer has been our unwelcome companion for all of human history. Yeah. Ancient medical descriptions of tumors and fossilized hominid remains with probable cancerous growth. They defy the labeling of cancer as solely a disease of modernity.

EAU: Mm-hmm.

EW: And yet, despite millennia of human evolution, despite the recent decades of cancer research, despite the thousands who have devoted their lives to finding a cure, despite the hundreds of thousands and millions who have also participated in finding this cure. Right. We still struggle to effectively treat or. Or even define this disease. Yeah. Why?

EAU: Why?

EW: To answer that we have to rethink cancer from an entirely different perspective. Yeah. Rather than seeing cancer as the single entity that can only be defeated through a full scale attack, we can use evolution to grasp the nuance and complexity that drives cancer development. Mm-hmm. Which hopefully will also steer us away from that military language of wars and battles, implying winners and losers and us versus them.

EAU: Yes.

EW: As you just explained, Erin, cancer cells are a part of us.

EAU: Mm-hmm.

EW: Why would cancer grow so out of control if that results in the death of its host and thus the cancer itself?

EAU: Well,

EW: why is cancer so common in humans? Shouldn't we have evolved to resist it?

EAU: Mm-hmm.

EW: It just doesn't make sense.

EAU: I mean, does it though,

EW: then again, paraphrasing, Theodosius dub jansky, nothing in cancer biology, he says nothing in biology. Yeah. Makes sense. Except in the light of evolution. Evolution, I, I challenge you to find a paper on cancer evolution that

does not reference ob jansky quotes, essay that quote. Yeah. So let's shine that evolutionary light on cancer.

EAU: Mm-hmm.

EW: This is a story told in four parts.

EAU: Okay.

EW: The first deals with seeking to understand the [00:40:00] evolutionary drivers of cancer cells. Why do they proliferate? Why do they spread? The second involves the defenses that we have evolved to prevent or control cancerous growth. Mm-hmm. The third scans for patterns across the animal kingdom in cancer resistance and susceptibility. Okay. And the fourth and final part asks, how can we apply this evolutionary knowledge to design better strategies for cancer treatment today?

EAU: Ugh. Erin, I can't tell you. I've been waiting for this episode for so long.

EW: This episode really was like a shift for me. Yeah. In being like, oh, this is not some, I know you called cancer or parasite. Mm-hmm. But it's not. Mm. Like it is just a product of evolution.

EAU: Mm. I love it.

EW: It doesn't want to survive. It just does because it happens to have evolved those certain traits.

EAU: Okay. Give it

EW: to me anyway. Okay. So part one.

EAU: Okay.

EW: When it comes to the deep evolutionary roots of cancer, our hominid fossils reveal the mest tip of the iceberg. In fact, even older specimens with suspected cancers on the order of tens of millions of years, like in the case of Duckbilled dinosaur fossils, which show cancer mm-hmm. To hundreds of millions of years, we're still in iceberg tip territory. Okay. The true origins of cancer extend back to the first multicellular life. When Life on Earth began roughly 4 billion years ago, single celled organisms ruled the roost, and they did

so for the next 2 billion years. During that unfathomably long period in which individual cells battled individual cells, cancer did not exist.

EAU: That is so, I mean, like

EW: it couldn't, it

EAU: could not exist.

EW: It could not exist, no. Because by its very definition, uncontrolled growth of abnormal cells, cancer requires other normal cells to stand out. In contrast.

EAU: Mm-hmm.

EW: Uncontrolled growth is only uncontrolled in comparison to what is considered controlled.

EAU: Right.

EW: So it was only 2 billion years ago when cells began to coalesce and coordinate to form multicellular organisms that cancer was possible.

EAU: Wow.

EW: Multicellularity, it's a great strategy. It's a great way to go, right? Yeah, it works

EAU: pretty well.

EW: I mean, imagine instead of doing everything yourself, you divvy up tasks like cleanup or resource gathering, and you can accomplish much more than you could on your own. It's true what they say. There's strength in numbers. Uhhuh. Multicellularity depends on cooperation on a massive scale. Mm-hmm. We like to think of ourselves as individuals, as individual thinkers, you know, with our own lives. So unique lives, so unique, but really what we are is a massive population of cells with different jobs and locations and genetic identities, and not all are human cells. Mm-hmm. We've got lots of non-human, tons of non-human

EAU: cells, possibly more than our human cells,

EW: possibly. This cooperation is really quite astounding. Mm-hmm. If you think about it. In her book, the Cheating Cell, uh, researcher, Athena Eist presents what she calls the multicellularity playbook.

EAU: Okay.

EW: I like this. In contrast to like, think about this in contrast to the, the hallmarks. Okay. Of the cancer hallmarks. Right. Hallmarks of cancer. Number one, don't divide out of control.

EAU: Mm-hmm.

EW: Number two, self-destruct if you're a threat.

EAU: Yeah.

EW: Number three, share and transport resources. Mm-hmm. Number four, do your job. Division of labor.

EAU: Yeah.

EW: Number five, take care of the environment.

EAU: Ugh. If only we could all

EW: basically just, I know.

EAU: Follow the rules of multicellularity.

EW: I mean, you

EAU: listen,

EW: there's too much. We can, I know, even go into there, but basically it comes down to do your job, be respectful, and everything's gonna be hunky dory.

EAU: It's all, we're all gonna be chill and living together. That's

EW: great.

EAU: Clean your dishes outta the sink. Put them in the dishwasher.

EW: Just, is

EAU: it that hard?

EW: Pick up after yourself. Yeah. And of course we know that things don't always go that way.

EAU: No, they don't.

EW: They rarely always go that way. Cooperation is vulnerable to exploitation by cheaters, and when cells don't follow the multicellularity playbook, cancer can result.

EAU: Mm-hmm.

EW: Cancer cells, they're not consciously cheating and intending to get a leg up on all these cooperative suckers. It's simply evolution. So our cells, as you said, are constantly replicating to grow, to develop, to replace damaged cells, and this process involves copying the DNA within our cells. With all that copying, a few errors are bound to slip in there. Yeah. Most of the time we've got these self-defense mechanisms or these little checkpoints, those mistakes are, or to, to make, you know, check up on things. Right. Maybe the mistakes are harmless, maybe they're repaired, or maybe the mistakes are too big and the the cell is self-destruct. Earmarked for destruction. Exactly. Yeah. But on occasion, those mutations will slide under the radar. Mm-hmm. And let's say that one of those mutations tells the cell to proliferate rapidly with no off switch. Another maybe helps it, uh, evade the defense mechanisms, whose job it is to catch these out of control cells. So now [00:45:00] we've got this renegade cell with the gas pedal to the floor and the breakout of commission. Mm-hmm. In no time that cell becomes two, then four, then eight, then 16, and so on. And

EAU: that's how cell division works.

EW: Yep. And all of these daughter cells are then inheriting those same mutations. Mm-hmm. These cells, they're not playing by the rules of multicellularity playbook. No. And in an evolutionary sense, they're doing great. Yep. There's no conscious thought to, like, I wanna evade, I wanna take these resources. No. Oh, that's a new resource. Let me take that. It's the cells that happen to evolve, the mutations that allow them to take advantage of this environment.

EAU: They are just growing because they can, they're just growing. Grow.

EW: Yep. Yep.

EAU: That's it.

EW: And spread.

EAU: And spread.

EW: Yeah.

EAU: Because they can,

EW: it's because the mutations evolve. Yeah. And so ultimately, if this proliferation continues unchecked, it will result in the death of the entire organism. Mm-hmm. Which includes the cancer cells themselves,

EAU: which is a bad thing.

EW: Right? So we've got these cancer cells, outcompeting normal cells. But if that ultimately kills the organism, how can that be evolution? Like isn't that just a dead end? It is. It's for that individual cancer. Yeah. Which will go extinct when its host dies. Yes. Extinction is not a new concept. And this is also asterisk for if you're a transmissible cancer. Right. Another story, that's a whole nother story. But like, dinosaurs have gone extinct.

EAU: Yeah.

EW: Humans have killed off many different species. So

EAU: many

EW: species

EAU: we have made go extinct

EW: in, you know, how many thousands of years. Yeah.

EAU: It's, it's part of the process of evolution.

EW: It's part of the process of evolution. Right. And I think it also is important to remember that evolution works on different timescales.

EAU: Yes.

EW: Yes. So to quote from Actis is the cheating cell quote. From the perspective of our bodies, cancer is a threat to our survival and wellbeing from the perspective of the cell. Cancer cells are only doing what every other living thing on this planet does. Mm-hmm. Evolving in response to the ecological conditions they are in, sometimes in ways that are detrimental to the system of which they are apart. End quote. It's just,

EAU: it's just

EW: evolution. It's, it's just evolution. Yeah. And I, I'm not, we're not saying that to minimize it. No, but just to explain like, this is not some, you know, parasite that's coming in and wanting to take advantage of this and doing this and that.

EAU: But I mean, even parasites are just evolution.

EW: Yeah, exactly.

EAU: Right. Like, right, right. That's the thing. They're not like, they don't have agency. They're not trying to kill us. It's just that they are, those particular cells are surviving.

EW: They're surviving. That is

EAU: all they are doing.

EW: And the ones that do survive are the ones that have the right. Characteristics,

EAU: the right tools, the right characteristics

EW: in that particular environment.

EAU: In that it's that environment at that time. Yeah. Yeah,

EW: yeah.

EAU: And and evolution is working on that population of cells,

EW: right? So 'cause cancer is not a one-time event.

EAU: No.

EW: Those renegade cells will continue to evolve as long as there is genetic variation, which is why we see diversity within tumors. Mm-hmm. Nor is cancer, just cancer cells. Mm-hmm. The tumor microenvironment both influences and is influenced by the cells that comprise it, both cancerous and non-cancerous. Mm-hmm. There's collagen to hold the tumor together. Blood vessels that deliver resources, even immune cells that have been reprogrammed by the cancer cells to tell other cells, don't worry about it, just move along. Some cancer cells might be more clonal, so like genetically identical than others, but genetic and tissue diversity is a feature of cancer, which is what makes it so difficult to treat.

EAU: Mm-hmm.

EW: Cancer is not a homogenous tissue. No. It is instead an evolving dynamic mass of genetically diverse cells. Yep. Within that mass, some cells might be super susceptible to a type of treatment, while others are more inherently resistant. If that treatment is administered, you would expect the resistance cells to increase in number because those are the ones left over. This is why resistance emerges so often after cancer treatment. Mm-hmm. And why oncologists combine different treatments. Right. And again, these cancer cells, they're not replicating uncontrollably or evolving resistance because they're evil or want to succeed, or they're

EAU: trying to kill you.

EW: They have simply inherited the instructions to do so. Mm-hmm. Part two,

EAU: okay.

EW: Defense against cancer. That chaotic growth, the seizing of resources, the resistance to destruction. These are not new weapons created by cancer cells. These are all qualities that are normal cooperative cells already possess. Yeah. If these features can do such harm when expressed in a cancer cell, why do they evolve at all? Because proliferation and differentiation are foundational to our growth and development. When we're growing as embryos, then fetuses, then infants healing a wound, fighting an infection, going through puberty,

reproducing, replacing the lining of our intestinal tractor skin. Proliferation, differentiation, movement and resource utilization. These are what makes us multicellular organisms. Mm-hmm. [00:50:00] If our cells exert too strong of a control over these processes, our development or our fertility might be negatively impacted as a result. Mm-hmm. So think back to our second episode in our pregnancy series when we talk about the placenta. Yeah. And there's this like kind of push pull where it's like, this is a really challenging, uh, experience for your body to be like, okay, this thing is growing inside me. And it's kind of like me, but it's not quite me, but it's like me, not quite like me. And so how much do I give and take? And what, it's a little bit of a balance there. Right. And it's sometimes hard to strike.

EAU: Yeah.

EW: And so there's this thought that like. Uh, cancer is one of the costs of higher fertility.

EAU: Oh, that's

EW: so interesting. 'cause there's more tolerance for things that are like you, but not quite like you. A little off. Yeah,

EAU: just a little off. Right. Oh, that's super interesting,

EW: Erin. Right. It's a tightrope.

EAU: Yeah.

EW: So if these processes are allowed to continue unchecked though, cancer might be the outcome. So it's either you are hold, you know, too tight of a control over them. Right. And then you, you stagnation

EAU: Right.

EW: And under development, or not enough control,

EAU: and then you end up with cancer.

EW: Yeah.

EAU: Oh, that's so interesting.

EW: Yeah. Yeah. This is the crux of cancer. Mm-hmm. The constant tightrope walk that we do as organisms to balance chaotic growth with stagnation. As actus puts it, quote, this leads to the counterintuitive conclusion that the optimal level of cancer risk for an organism is not zero.

EAU: Right.

EW: Yeah. End quote. That is the, to me, that's like the bottom line of everything. Yeah. That cancer is the consequence of multicellular life. Yeah. To, for growth and division reproduction.

EAU: Right. It's all of the things. It's part of it that we already do. It's just doing too much.

EW: Yeah. The near ubiquity of cancer across multicellular organisms demonstrates that cancer is an unavoidable consequence of complex multicellular life. One that can shorten lifespan and impact fertility to a considerable degree. Just because we have a multicellularity playbook doesn't mean everyone follows these rules, and so we've evolved different strategies to catch and eliminate those cheaters. Mm-hmm. The first is intrinsic. So ourselves, you'd kind of talked about this ourselves, contain within them these intrinsic mechanisms to monitor for any funny business, big mistakes in DNA transcription, wonky proteins, or something else that signals that this cell might not be following the multicellularity playbook. If something abnormal is detected, that information is processed, and then a quote unquote decision is made. There's no conscious thought here. Right, right, right. Just using it as a shortcut. Yeah. Can the cell be repaired?

EAU: Right.

EW: Should we shut down replication until the error is fixed? Should the cell self-destruct? Mm-hmm. This is where something like TP 53 comes in, our famous tumor suppressor gene, also known as the guardian of the genome, which I. Really love. I

EAU: know.

EW: And so it

EAU: sounds so noble.

EW: I know. Helpful. So TP 53 takes in all this information and it initiates the appropriate response. And that's just one example, right? Of our intrinsic defenses against cancer. We've got many other strategies like preventing or repairing DNA copying mistakes in the first place. Exactly. And then in addition to these intrinsic mechanisms, we've also got the neighborhood watch. This is pretty much what it sounds like. Cells keep an eye on their close neighbors for any sign that something suspicious is going on. Looking little binoculars through the window. Like what time is it? It's

EAU: just like that. What's that app? Who's coming that everyone's using?

EW: Next door.

EAU: Next door.

EW: Yeah. It's just, it is. It's just, just like that. Yeah, it is. And so for the most part, our cells are quite sensitive to self-destruction. Yeah. You just give them a funny look and they're like, okay, fine. I guess I'll just self-destruct. Yeah. They're committed to cooperation and so often it's, it's not so much like that the neighbor cells have to be like self-destruct. It's more just like if the neighbor cell is like, uh, you're not. You're not really pulling your

EAU: weight,

EW: man. Right. Like they want constant positive reinforcement.

EAU: Yeah.

EW: And so if their neighbor cells like, I'm just, it's not, it's not doing it for me.

EAU: It's not, it's not me, it's you.

EW: Right. Then they're like, okay, I guess I'll just self-destruct. I'm here. Okay. Yeah. And, um, and the neighbor cells will eventually be like, you need to self-destruct gets, if it's like, if they're like, come on, take a hint. So, okay. So our cells have got these internal monitoring systems. They, their neighbors are keeping a watch on them. And then there's this more global line of defense, the immune system. Right. Our immune system is constantly scrutinizing cells for any signs of cheating, like excessive proliferation, consuming too many resources, and avoiding instructions to self-destruct. And one of the ways our immune systems do this is to detect tumor antigens, which are these proteins expressed on the surface of certain cancer cells that the immune system reads as

a signal that the cell is behaving inappropriately. Yep. And if they detect one of these antigens, they can tell other cells search and destroy. Yeah. Anything expressing this antigen, it's basically like what they do to viruses. Exactly. Destroy, yeah. So these three primary means of cancer suppression are continuously monitoring for any signs of trouble. And when you think about the 30 [00:55:00] trillion or so cells in our body, I have a citation for that.

EAU: No, yeah, I saw 30 to 40.

EW: Yeah,

EAU: yeah,

EW: yeah.

EAU: It's bananas.

EW: And I was like, it is also brilliant. To write this paper, you'll be cited so frequently. 'cause everyone's gonna be like, how many cells body, how many cells are trillion? Lemme find it, lemme find it on Google Scholar. Yeah. Um, but when you think about all these cells, it's, it's pretty astonishing how good of a job our body does most of the time when it comes to monitoring for any signs of disruption.

EAU: Seriously. And like if you really know how many times we make mistakes in DNA replication.

EW: Yeah.

EAU: It is fascinating that it doesn't, that cancers and other deleterious mutations don't arise more frequently.

EW: Right. I mean, and this is a reflection of millions of years of evolution. Yeah. Billions. When we look at an age distribution of cancer diagnoses most happen later in life. Mm-hmm. And comparatively and comparatively few happen in childhood, despite childhood being a time of rapid cell proliferation and differentiation. Mm-hmm. As we grow and mature, right, there is stronger selection for those cancer suppression mechanisms at an early age. Ah, that makes sense. Because the cost of cancer through an evolutionary lens, like the fitness cost is greater. That selection relaxes a bit as we get older. Mm-hmm. And to be clear, I'm not suggesting that it's worse than when cancer happens in a child compared to an adult. Cancer is awful no matter when it happens. Mm-

hmm. I'm simply saying that these cancer defense mechanisms were more likely to be passed down because they conferred a benefit for survival and reproduction, especially earlier in life.

EAU: To our whole organism.

EW: To our, our whole organism. Right? Yes. Yeah. Remember, again, it's a tightrope. These defense mechanisms don't always function perfectly because there's a trade off between chaos and stagnation. Mm-hmm. If having a bigger body means better survival or reproductive viability, then you don't wanna restrict proliferation or differentiation too early. No. Same with wound healing.

EAU: Mm-hmm.

EW: Same with tissue repair, making new blood cells and so on. How do different species balance this trade-off? Like what patterns exist? Part three.

EAU: Okay.

EW: Cancer across the animal kingdom.

EAU: Okay.

EW: Uh, there are cancerous growths in plants and

EAU: Yes.

EW: And fungi. I'm not gonna talk about them. They're

EAU: so interesting and cool looking

EW: though. I know. They're very cool. Yeah. But it's, that's too big for

EAU: Oh yeah.

EW: This is already too big. Are you kidding? Yeah, I know, I know. Uh,

EAU: but it is true. It's all multicellular organisms and that

EW: includes plants. Yeah. Yeah. Almost all. I read some stuff about sponges that I, I took out, but anyway. Sponges though, they just sort of like pinch it off and they're like, disease. They're like,

EAU: you

EW: don't need anymore disease by. Yeah. Yeah. That's cool. Uh, kind of like what our guts do a little bit. It's, it's very cool.

EAU: Yeah.

EW: So, uh, knowing what we know about cancers, what are some patterns we think we might find? Yeah. Okay. Broadly speaking, cancer happens when a cell acquires mutations that A, let it throw out that multicellularity playbook and b, escape detection and destruction by cancer suppression mechanisms. It takes for cancer to develop is one cell going rogue and the red environment and not

EAU: everything else. Yeah, but,

EW: but you know what I mean. Exactly. You still need the initial, you need that. You need the potential.

EAU: Yes.

EW: Yeah. So you might expect that the more cells there are, the greater the risk of cancer.

EAU: Do we see that, Erin?

EW: Mm-hmm. Okay. So if this were the case, what we might expect to find is that elephants, blue whales, rhinos, and other large bodied species should have higher rates of cancer. More than small ones like mice, bats, small birds, and longer lived species like giant tortoises. And humans whose cells have a lot longer to accumulate cancerous mutations should also have a higher risk of cancer compared to those with relatively short or comparatively short lifespans. Okay. Like shrews and hedgehogs.

EAU: Okay.

EW: That's not what we find

EAU: interesting.

EW: Yes. In fact, there seems to be no correlation at all between longevity, body size, and cancer across species.

EAU: Huh?

EW: This surprising finding has a name. It's called Petto Paradox.

EAU: Oh, I've heard of this.

EW: Okay. Yeah, yeah, I know.

EAU: Petto Paradox.

EW: Petto Paradox. So elephants, despite having 100 times the amount of cells that humans do, do not have 100 times the risk of cancer.

EAU: Yeah.

EW: In fact, elephants are less likely to develop cancer compared to humans.

EAU: Interesting.

EW: On the other end of the scale, mice are more likely to develop cancer than humans are.

EAU: Really,

EW: really?

EAU: No one talks about that.

EW: I know.

EAU: Not just the mice we grow in labs. I presume.

EW: I don't, I mean, so this is where, don't get me started on like the data viability. There are multiple papers that discuss about like the limitations of Petto paradox and the observations that have been used to formulate anyway.

EAU: Okay.

EW: So, however, though within a species, the pattern is there, the expected pattern that we see. So bigger dogs are more likely to develop cancer than smaller dogs. Taller humans are more likely to develop cancer compared to shorter humans. Uh. The same goes for age. Okay. Again, within a species.

EAU: Okay.

EW: Yeah.

EAU: How interesting.

EW: Yeah. So why might this pattern [01:00:00] not hold across species?

EAU: You gotta have, they gotta have something else going on.

EW: There's gotta, I mean, there's

EAU: some other protective mechanisms,

EW: many different possible answers, right? Yeah. Larger species might have lower mutation rates overall.

EAU: Mm-hmm.

EW: They might have more tumor suppressor genes. This actually has been found in elephants who have 20 copies of TP 53, mind compared to humans. Two copies.

EAU: I learned that once.

EW: Yeah.

EAU: I knew that once I learned that, obviously forgot it. But I learned that once it's, it

EW: blew my mind.

Yeah, yeah, yeah. It blew my mind. Uh, there maybe the, there's a species immune systems could be more tuned into precancerous or cancerous cells.

Their cells might be more sensitive to a self-destruct signal. It's even been suggested that larger animals develop larger tumors that then themselves are destroyed by cancerous cells. Where it's like. Tumor infighting. Interesting kind of thing. Okay. Like there's something about like, yeah.

EAU: Just then the way that it interacts with their immune system is gonna

EW: be different. Something like that. Yeah.

EAU: Okay. Interesting.

EW: So in short, yeah. There are a number of different hypotheses as to why larger bodied and longer lived species have less cancer than we'd expect. Okay. Pet's paradox might also reveal different trade-offs in life history strategies. So take a mouse for example, which matures to reproductive age pretty quickly to take advantage of that quick development time. You might wanna step on the proliferation gas, right. So to speak, even if that comes with a higher risk of cancer. Mm-hmm. Mm-hmm. And this is actually what we have found when it comes to chicken farming. Chickens that are selected for early egg laying and higher production tend to have higher rates of ovarian cancer.

EAU: Oh, interesting.

EW: Mm-hmm.

EAU: Because they're like, make more eggs, make more

EW: eggs, make more, make more proliferate, proliferate, proliferate. And elephants, which mature later on, might invest more in cellular watchfulness.

EAU: Mm-hmm.

EW: Earlier in life.

EAU: Interesting.

EW: Uh, just to make sure that they survive to reproductive age. Right. Of

EAU: course.

EW: So Pet's paradox has been revisited repeatedly since it was first introduced in the 1970s, and researchers have argued that there is no paradox if you analyze the data this way or the paradox grows stronger if you analyze it that way, or depending on where you're getting your data on all this stuff. Right. But there seems to be no getting around the observation that from the existing data that we have, cancer risk is lower than we would expect in larger bodied and longer lived species. Okay. Beyond Pedos Paradox, there are a few other patterns that researchers have observed. Birds and reptiles tend to have less cancer than placental mammals. Species in carnivore mammals that eat flesh tend to have higher cancer risk. This might be because of bio magnification. So like carcinogenic compounds have accumulated the top of the food chain. Mm-hmm. A low fiber and high fat diet and Yep. Potentially cancer causing pathogens found in raw meat.

EAU: Interesting. Okay.

EW: Yeah.

EAU: Cool. Cool.

EW: Uh, deer, uh, uh, that grow large antlers every year, rapid cell rapid proliferation. Proliferation tend to have higher rates of cancer. And there's some other stuff about like sexually selected traits like that, that involve Oh, that's so interesting. Big things. Yeah. And species that have undergone a genetic bottleneck, like the Santa Catalina Island foxes mm-hmm. Tend to have higher rates of cancer. Prevalence for them is like greater than 50%.

EAU: Really.

EW: So that suggests that genetic diversity, especially when it comes to immune diversity, is really important when it comes to being protective against cancer.

EAU: I, there's so many levels that I'm loving this Erin, but also just, I feel like I have seen on the internet people being like, but cancer only happens in humans.

EW: No, no,

EAU: no. And like just the diversity already that you've said,

EW: oh, there's, yeah,

EAU: I know, I know, I

EW: know.

EAU: You know the internet.

EW: I know, I do know the internet, if I'm familiar,

EAU: you've heard of it,

EW: I've heard of it. We're quite close. There's also other environmental or developmental drivers that could play a role in cancer risk across species. You know, if you're a species that's, if that's, uh, exposed a lot to UV radiation, maybe you're more likely to get cancer, maybe you're more likely to evolve defense against defenses

EAU: against that kind. Yeah. Yeah.

EW: Alright. Uh, the rate of healing might be positively associated with cancer risk. Makes sense. So if you're a fast healer.

EAU: Right.

EW: You might have higher risk of cancer

EAU: because again, the like immune system mechanisms and the inflammatory process and the wound healing process uses a lot of those same features that cancers exploit.

EW: Yep.

EAU: Kind of a thing.

EW: Yep. Yep. And this is by no means an exhaustive list of the patterns that we see in cancer risk across the animal kingdom. Yeah. Nor does it fully explain the lifetime cancer risk in humans of 40%. Because even though we have these mechanisms that lower our risk of cancer, they don't take it to zero. And we talked about why that's probably not possible, right? Mm-hmm. The ideal risk for cancer is not zero from

EAU: an evolution,

EW: from an evolutionary perspective when it comes to proliferation and differentiation. Right? But 40% might also reflect an evolutionary mismatch. Cancer is a consequence of multicellularity. Yes. But the environment that we live in now is different than the one in which we evolved.

EAU: Exactly.

EW: Things like cigarettes, processed meats, our sedentary [01:05:00] lifestyles, our increased longevity, all of these things lead to a higher risk of cancer. Alcohol, alcohol. And correspondingly, they, they lead to a need for a better approach to treatment. Mm-hmm. Part four.

EAU: Okay.

EW: How can we apply what we know about cancer evolution to design treatments that outmaneuver rather than outright attack cancer? Mm-hmm. Even if you had never heard of treatment resistant cancer before, the concept of resistance would probably be familiar to you, right? Right. Antibiotic resistant bacteria like MRSA or pesticide resistant insects, show us that resistance is a useful and expected trait that emerges in a biological target after a powerful onslaught

EAU: in the context of evolution. Erin,

EW: in the context of evolution, it's the same old story, right? Yeah. You, you get a, you target a susceptible population with some type of treatment. Maybe that's penicillin, maybe that's DDT. Maybe that's chemotherapy. Maybe that wipes them all out. Or maybe a few invulnerable individuals remain. Those few multiply into many, and now you've got a fully resistant population against which you are powerless. Yep. This can happen in an individual receiving cancer treatment. Over time, the cancer may stop responding to those therapies, and this is a major issue in cancer that contributes to significant mortality every year. And we've struggle. We continue to struggle to contend with it. So faced with this substantial challenge, some cancer researchers have taken inspiration from other fields outside of cancer.

EAU: Cancer,

EW: like agriculture.

EAU: Okay.

EW: To devise ways to minimize the emergence of resistance in the first place.

EAU: Okay.

EW: One approach called adaptive therapy is modeled after integrated pest management.

EAU: I integrated pest management.

EW: Yeah. Yeah. Which is an agricultural, what? It's the robot I know. So integrated pest management is an agricultural technique that assumes resistance will eventually mm-hmm. Evolve. And so you delay the inevitable as much as you can. Mm-hmm. You utilize small doses rather than massive blast with a goal of long-term control rather than eradication.

EAU: Mm-hmm.

EW: Adaptive therapy, which is the, the cancer version of this, is intended to keep cancer cells sensitive to the drugs, and it has the added benefit of doing less damage to the surrounding tissue. Mm-hmm. The key is monitoring and adjusting the dose or timing according to how the tumor is responding. Mm-hmm. So if the tumor grows, you might wanna increase the dose if the tumor shrinks, lower the dose, or just stop giving some meds. If it stays the same, either, you know, keep the dose the same or back off a little. It works. I mean, it's basically like a thermostat,

EAU: right?

EW: You're just like, okay, how do we get to 72?

EAU: You're not trying to get rid of anything. You're just trying to not let it get any bigger.

EW: Yeah. And sometimes maybe getting rid of something means getting smaller, getting your immune system to step in. Mm-hmm. Mm-hmm. Sometimes it means just like slowing things down. Right? Right. And so by employing this approach, you're selecting for slower dividing cells and you're relaxing that pressure to develop resistance. Mm-hmm. And for resistance to be the key defining trait of this tumor now. Yeah. Resistance mechanisms can be really costly to maintain. So if there's no need for them, those resistant cells might be out competed by sensitive ones. Yeah. I came across a great analogy explaining this, that I really, I really like. So think about like a big, bulky

umbrella. Okay. So this is our resistance mechanism. Okay. It's heavy, it's annoying. You have to lug it around everywhere with you. I

EAU: always forget it.

EW: Always forget it. Yeah. If it's raining all the time, IE big doses of chemotherapy, the inconvenience is totally worth it. A

EAU: hundred

EW: percent. And you're probably not gonna wanna leave it somewhere.

EAU: Yeah.

EW: But if it's mostly sunny or just occasional drizzles, you're like, you're gonna forget at a cafe. Absolutely. And not think about it again. I'm gonna

EAU: just wear my raincoat.

EW: Right. It's

EAU: gonna be fine.

EW: And so resistance can also, like you can, cells can also evolve to no longer be resistant, right? If there's not that pressure to, to maintain resistance. So the beauty of adaptive therapy is that it's both generalizable and personal.

EAU: Hmm.

EW: Right. You can use this with any existing, theoretically. Right. Can use this with any existing drug or treatment and you're constantly tweaking the dose or timing based on how that individual tumor is responding.

EAU: Responding. And it could be with any drug, right. Any drug that initially shows a benefit.

EW: Yes.

EAU: You could do it with,

EW: you could do that with, yeah. Mm-hmm.

EAU: Hmm.

EW: So, sounds great in theory.

EAU: Mm-hmm.

EW: Is there any clinical evidence to back it up?

EAU: Tell me

EW: There is. Mm-hmm. The first clinical trial testing adaptive therapy was conducted 10 years ago in 2016 on people with metastatic prostate cancer whose cancer was no longer responding to hormone therapy. Mm-hmm. Those who received adaptive therapy had a median time to progression of 27 months. Okay. Compared to the 16 and a half months time to progression with standard treatment. Okay. So that's an extra 11 months, 10 months, 11 months. Yeah. That's huge, huge, huge. So it slowed tumor growth in that way. It, it [01:10:00] actually slowed the progression mm-hmm. Of the disease. Mm-hmm. And with adaptive therapy, the chemotherapy dose was cut in half suggesting that this approach could lead to fewer side effects and lower medical costs, which is a concern in this country. Mm-hmm. Since that first trial, a handful of others have begun on prostate and ovarian cancer and several of which are still underway or I think in the works right now. And, but even though it's, it's early days, adaptive therapy seems like a really promising area of cancer research. And it's important to point out that this is not for every case of cancer. Right. Some cancers are going to respond better to some therapies than others, and researchers have devised different criteria for determining when a cancer might be treated with an aggressive versus an adaptive approach. Like when what, what is going to result in the outcome that we most want, or like the ideal outcome. Yeah. But especially when it comes to cases where a cure seems unlikely, adaptive therapy may be able to control or delay progression. Mm-hmm. Another tactic is decoy drugs. Have you come across this? No. Okay. Love this. So these are used for treatment resistant cancers. Um, and I also don't, like, I haven't read extensively on the existing literature, but so like, this is more of like the, as it, the theoretical as it was explained in a theoretical basis. Yeah. Um, but resistant cells, so they've, there are some resistance that that involves. Evolving pumps to pump out the chemotherapy. Mm-hmm. Before it can do any harm because chemotherapy, I know we'll talk about it next week, but basically its goal is to kill cells. It's just

EAU: killing

EW: cells. It's killing cells, killing cells. And so it's like this is a toxic thing. Pump it that out. Out. Yeah. Yeah. And so the I, the idea with these, with these pumps is that they pump out the chemotherapy drugs before it can do any harm, and that's how resistance works. Okay. In those cells. These decoy drugs can take advantage of that.

EAU: Ah,

EW: they don't do anything to the cancer, but they appear like dangerous chemicals. Ah. So those cells continuously pump them out. They're like, oh my gosh, it's coming. It's gonna kill me. It's gonna kill me. I'm gonna pump it out, pump it out. This is constant work exhausts the cells. It depletes resources and it makes them expend too much energy to replicate. And so the goal with these therapies

EAU: is not to actually do anything to the cells except just keep them busy.

EW: Keep them busy. Yeah. So

EAU: interesting.

EW: Exhaust them. So it's, it's not, it's, it's not to eradicate, it's not to destroy. It's just to anticipate cancer's next move or even guide that next move.

EAU: How interesting, Erin,

EW: so for instance, there's one thought is that cancer cells become more likely to invade to a new area if their tumor environment becomes hostile or resource depleted. Like what would happen with aggressive chemo

EAU: and radiation

EW: and radiation. There's this idea that like maybe maintaining that tumor, and again, this is very dependent upon the individual, the cancer, but maintaining that tumor at that size, maybe that would prevent the cancer from spreading. So instead of shrinking the tumor, instead of attacking the tumor, we just keep it content. Keep it

EAU: how it, how it is.

EW: Yeah. So that the cells don't spread,

EAU: just don't let it do its invasion thing.

EW: Yep. Yeah. Or what if we directed evolution so that benign cells, quote unquote, were encouraged to grow over malignant ones? Hmm. How do you kind of do that? You can kind of lead it down and like into an alley and then trap it cancer in that way. I mean that, this is sort of the idea.

EAU: Yeah.

EW: We could also support our own body's ability to detect or eliminate cancerous cells, which I'm assuming you're gonna talk about next week.

EAU: Mm-hmm.

EW: Mm-hmm. It is. Extremely encouraging to see the incorporation of evolutionary principles into cancer treatment, and it's something that is long overdue. So there was an analysis published in 2011 where authors estimated that 1% of all papers about cancer recurrence or resistance that were published since the 1980s mentioned anything about evolution. 1%. Oh

EAU: dear.

EW: Talked about evolution. Ongoing research on cancer evolution, tumor ecology, and adaptive therapy. It holds the power to transform the way that we understand and treat cancer. And I'm really excited to see where this research will take us. Mm-hmm. But only looking back on the journey that brought us here. Can we appreciate how far we've already come?

EAU: Oh, this is so true, Erin.

EW: So stay tuned for next week when we talk about cancer treatments.

EAU: Another great cliffhanger.

EW: Thank you. Thank you.

EAU: What a journey, Erin.

EW: I I just, it really helped me to think of cancer cells as just successful in an evolutionary context. Yeah. Using the tools that they already had.

EAU: Yeah. Yeah.

EW: In our normal cells,

EAU: which I honestly still like, that is why I, they, they seem like a population of bacteria to me.

EW: But like, but they're not, I, I know, I know

EAU: because they're us,

EW: but it's us and

EAU: so they have all of our traits and all of this,

EW: but, but bacterial cells have, you know, certain toxins or certain whatever.

EAU: Right. Right. They have other things that they, and we don't. Right.

EW: And they're, they, they don't, the cancer cells are working with the toolkit

EAU: Yeah.

EW: That every single one of our cells already has. Yeah, yeah. Yeah. True. That what blows my mind.

EAU: Yeah, yeah,

EW: yeah.

EAU: It's true.

EW: Yeah,

EAU: [01:15:00] it's true. They're just acting like they're not a part of us.

EW: Right. Yeah. They're like, well, I mean, I'm just, yeah. I have this, this new trait, so

EAU: Yeah.

EW: Sorry.

EAU: Sorry.

EW: Can't help it. It's better for me.

EAU: Yeah.

EW: Yeah.

EAU: It is so interesting.

EW: But

EAU: yeah. Well, next week we'll have a lot more for you, but if you want to read more. Who, boy.

EW: Oh yeah, we do.

EAU: We sure

EW: have a lot of sources. Oh, guess I always go first. You do, yeah. Thanks. Just gesture to you. Mm-hmm. Uh, okay. So it. I, the the Cheating Cell by Athena Actus. I thought it was absolutely fascinating.

EAU: Love it.

EW: Great, great. Dive into evolution. I almost read

EAU: evolution and then I was like, oh, I think Erin is reading that. So I'm gonna not,

EW: it's 'cause we're friends on. Good read. Uh, then there's a paper by Colin and Mally, uh, pet's Paradox, evolution's Prescription for Cancer Prevention from 2011. And then if you want to read sort of a nice little overview of adaptive therapy by Zang et all from 2023 in critical reviews in oncology, hematology.

EAU: Love it. I have a, uh, a good number of papers for this episode. I think a couple to shout out. There's like three papers going from 2000 to 2022, um, by

Hannah, Hannah, and Weinberg. And one is just by Hanahan that are like called the Hallmarks of Cancer. So those are kind of like the classic.

EW: I have a few of those.

EAU: Yep. Yeah. And then there's a couple that are like pushing back against the hallmarks of cancer, which like, I don't think change things all that much, but I have a few of those as well too.

EW: Catchy title though.

EAU: Yeah. They got, they got me. Um, but, but some of them are good and they really just talk more about the microenvironment. So one of them that I particularly liked is over a century of cancer research, inconvenient truths and promising leads by Sauna, shine, and Soto from 2020. But again, there's a bunch more. Um, I don't even know which other ones to shout out. There's so, there's, there's so, so many, um, lots more on the mechanisms of carcinogenesis from environmental things. If you want that, you can find them all on our website.

EW: Yes.

EAU: This podcast will kill you.com.

EW: It's truly a massive list. Happy reading. Happy reading everyone.

EAU: You're welcome. Everyone writing their term paper. It's like, thank you.

EW: I mean, seriously though. Yeah.

EAU: Seriously. We did it for you. You're welcome.

EW: Yeah. So, uh, thank you. Thank you also to the providers of our firsthand accounts again. Yeah. What, what can we say that hasn't already been said? Thank you. From the bottom of our hearts,

EAU: it's, we can't thank you enough is the truth of it. So thank you. Thank you, thank you. Thank you.

EW: Um, I'm gonna say thank you again to Blood Mobile. Yeah. In addition to Jon and Brett for

EAU: Yes. Those are our husbands. We thanked them before.

EW: And Blood Mobile. My brother,

EAU: blood brother for the music.

EW: For the music.

EAU: Yeah. We really appreciate you.

EW: Yes,

EAU: we

EW: do.

EAU: Uh, thank you to everyone here at the exactly right studios. Everyone. Thank you. Thank you. Thank you to Tom and Leanna and Pete. Thank you to Jessica and Sabrina and Boomer. We're gonna thank everyone today. I remembered names.

EW: Oh my gosh. We've

EAU: got this.

EW: Uh, so many thank you to go around. Thank you to our listeners, thank you to our patrons. You all make this possible.

EAU: I hope you guys enjoyed this episode.

EW: Yeah,

EAU: I did.

EW: Yeah.

EAU: It's really,

EW: tell us what you think.

EAU: It's interesting. We've got a lot more coming, so make sure you subscribed

EW: and until next time, wash your hands.

EAU: You filthy animals.