# Why and How We Get Cancer – Transcript

By Jeremy Shaw

*Intro*

Imagine I handed you a full piece of paper covered in letters with no spaces and asked you to make an exact copy as fast as you could. That would be pretty hard right? Now imagine if instead of that one piece of paper that you had to copy a few more… like enough to fill over 1,000 bibles or almost 1,350 dictionaries. Now even if you were amazing at copying these letters accurately, let's say you only mess up 1 single letter out of every 21 pages. But that means over the course of copying all of those pages, you'd make 60,000 mistakes. Luckily for you though, you have a proofreader that is not only constantly looking over your shoulder, but can also go back and find mistakes later and fix them! Although that proofreader sounds like one serious micromanager, they are also Very good at their job bringing your total number of mistakes from 60,000 to just six! Now six mistakes out of all of those 1,350 dictionaries of pages sounds awesome, but they are still mistakes. Now maybe some of these will be lucky and not mess anyone up! For example, maybe you messed up a letter in a word that no one will ever read or isn't read very often, like xylophone. Or maybe you accidentally spelled barbecue with a q instead of a c.. No big deal! But sometimes you can make a word not make sense anymore like changing "the" to "xhe". Or even worse, if you accidentally change the P in pill to a K… you could cause some serious issues when someone wants their medicine, holds out their hand, and says "Pill me" What's also unfortunate is that once the mistake is in that set of dictionaries, every time you copy that set, you'll copy that mistake to new sets as well!

So if you understood all of that, great! You now know 85% of how we get cancer! So let's go back and change some words to make it sound more "science-y"

But before we do, 30 seconds of background! So almost every cell in your body contains your all of your DNA, your whole 3 billion base pair genome. So think of base pairs as two matching letters and your GENome just refers to all of your GENEs which are small units of your DNA with specific functions. Your DNA, and thus, your genes, contain all of the information that tells different cells in your body what to do, plays a large role in determining eye color, height, weight, etc. and no two people have identical DNA (not even "identical" twins).

So your cells are the little pieces of you that make up all of your organs and pretty much every other part of you! Anyway, if <u>any</u> of the 37 trillion cells in your body need to divide, they have to copy their whole genome… twice! ..Just to divide One time! Now for some of your cells that barely divide, if ever, that's not a big deal! For example your cardiac/heart cells, neurons, and some types of muscle never divide, so they don't care about the difficulty of making a copy of all of their DNA! (Remember these cell types, we'll come back to them!). However, other cell types like the lining of your intestines, your non-red blood cells, and your skin cells need constantly replaced. We lose about 50 million skin cells every day, and likely over trillions of gut cells, so yeah, we have a lot of cells to replace! These cells can be replaced by other cells dividing and forming "daughter cells".

Ok, so let's combine our cellular world and the big world scenario we set up earlier now that all the background is done. Side note - Don't worry about all the terms I'm about to use, I won't use them again, but I'm using them so you have em if you want!

So now you're a cell in the small intestine that has to divide! You have 3 billion base pairs in your genome (675 dictionaries of letters) to copy: Twice -once for each new cell you are forming- before you can divide (now that's 1,350 dictionaries). You're efficient, but you make one mistake every 100,000 letters (every 21 pages). However, these mistakes are fixed by DNA polymerase editing (your boss pointing out mistakes as they happen) or by exonucleolytic editing (your boss going back and fixing your mistakes afterwards). Now you still have about 6 mistakes in your DNA, but some of them can be in genes (words) which aren't used very often (like xylophone). Other gene mutations can be silent and not change anything (spelling barbecue with a q instead of a c). Other times, though the gene (word) can no longer be recognized or work (changing "the" to "xhe"). Or even worse, it have a completely new, unintended function (like changing Pill to Kill). If that error (misspelling) does get by without being corrected, now every time you divide in the future, all of your "daughter cells" (All future copies of that dictionary) will carry that same error. Additionally, all of Their daughter cells will have it and all of Their daughter cells will carry it as well, and so on and so forth (all future copies of the dictionary will have that mistake).

Phew! OhhhhhKay! So you still with me? That's most of the hard stuff! Now we just have a few more important things to understand and you'll be an expert on Cancer Biology! Right now you're probably wondering, "Jeremy, what does a misspelled word or mutated gene have to do with cancer, how could that possibly cause it??" That's a good question! To answer that, let's go back a looonnng time ago! How old are you? ______ ok, so that long! Actually, we need to get back a few months before you were even born to understand! So all humans start out as just a couple of cells. And how do you turn from those few cells into that beautiful person you are today? You need to Grow like crazy! Your cells activate genes called "Proto oncogenes" these genes help your cells quickly grow and divide, think of proto oncogenes as a gas pedal. It's how you go from just one cell to billions when you're born 9 months later. However, when you become an adult, you no longer need to do things like grow a new liver from scratch or just keep dividing and dividing to form bigger bones. Thus, you want to shut down these genes by taking your foot OFF the gas pedal when you're an adult.

On the other side of the coin are the "tumor suppressor genes", care to guess what they do? ___Yup! They suppress tumors, you're crushing it, gold star! Think of them as the breaks in the car.. And probably the most important thing you'll learn about here. If there is something wrong with the car (cell) the tumor suppressor genes will use the brakes to stop the cell from growing and dividing. If the problem can't be fixed, the tumor suppressor will cause the cell to die. Now although a cell killing itself may sound bad at first, it is better to have one less cell than one more potentially out-of-control cell. Now there are many, many other genes as well as many types of proto-oncogenes and tumor suppressors, but for simplicity's sake.. Let's keep it narrowed it down to these two genes for now. Remember, proto-oncogenes need to be off and the tumor suppressor genes need to be on.

You remember all of those dictionaries you were copying earlier? So let's say one of those 6 mistakes, or mutations, in your cell was in a proto-oncogene. This can cause the proto-oncogene that was turned off to be turned back on. This "activating" mutation of a proto-oncogene, turns it into an oncogene. Basically, you're dropping a brick onto the gas pedal so the cell just starts growing and growing.
Luckily for us, we have our "tumor suppressor" gene that can normally pump the brakes and stop the cell from growing, likely killing it. Unfortunately, not all outcomes have such a happy ending. If one of the 6 mistakes was in a tumor suppressor gene first, turning it OFF, and then another mistake from a daughter cell (a copy of the first set of dictionaries where it was already turned off) turned the oncogene on, now the cell can grow out of control. When these cells start growing where and when they shouldn't, they can form an abnormal mass of cells, aka, a tumor. A tumor doesn't necessarily mean cancerous, though. I've got one more car analogy to help you tell difference.

We've talked about how slamming the gas pedal (making an oncogene by turning ON a proto-oncogene) or ripping out the breaks (turning OFF a tumor suppressor gene) can cause the car (cell) to go/grow go faster than it should.. But to be considered a cancer, the cells have to be "malignant" this means it needs to spread. Think of something turning the car's steering wheel causing it to go somewhere it shouldn't. Maybe it just turns the wheel slightly and goes from the road into woods nearby, spreading locally. Or maybe, it gets on a different highway and goes all the way to another distant state. This is similar to a gene that effects "migration" being mutated. (Again, there are many genes that effect migration, but I'll just generalize and call them migration genes here). Sometimes it will cause the cell to migrate and invade into another local tissue or muscle (off the road, into the nearby woods), other times, the cell will enter the blood stream or similar route (similar to getting on the highway) and travel to lymph nodes or another organ (state) far away. At any rate, this spread, whether local invasion or distant "metastasis" of the mutated cells is what can officially make them malignant, and thus, cancerous.

Ok, now I think you Really understand cancer biology, there are just a few final things I think are worth mentioning!

Firstly, you may be aware that cancer rates are on the rise. I haven't yet done the necessary research yet to exclude many possibilities, however, there is something very important you should consider before going gluten free or rubbing coconut oil under your armpits or whatever it is you're thinking about doing! I said that your cells may only have 6 small errors every time they divide. But as an example, if your cells divide every single day, then it isn't just 6/6 billion… it's 6/6 billion on Monday, then another 6/6 billion on Tuesday, and this accumulates for weeks and months and years and years and decades. Every time your cells divide you increase your chances of getting an error, every time you get an error, you increase the chances of it being something bad, every time it is something bad, you increase the chances of it being cancerous. Thus, the older you are, the more chances you've had in your lifetime to get cancer, this is why cancer is often referred to as "the disease of aging". Now that people are living longer thanks to everything from seatbelts to antibiotics to vaccines, more people are living long enough to get cancer. So kind of a double-edged sword..Yay?

Secondly, if you'd like some anecdotal evidence for what I've told you today, let's think for a moment. How many kinds of cancer can you think of? Name a few to yourself for a moment.____ So… was heart cancer on that list? Brain cancer might have been, but cancer in the brain either came from a distant site or formed from non-neuron cells in the brain. Do you remember what was special about heart cells and neurons? ____They don't divide. Now true, this is just a correlation not causation, but they are some of the only living cells/tissues that don't develop cancer likely because they're not dividing as much and have decreased chances of developing these errors or mutations.

Thirdly, I just told you that cancer was called a disease of aging; so why would children ever get it? Actually, you could probably already answer this. If I handed you a set of dictionaries where there were mutations or mistakes that had already turned the tumor suppressor off, that person would already be much more likely to get the other mutations now, right? In brief, that's essentially what happens. If a "bad copy" of a gene is either inherited or mutated early on, that person becomes far more likely to develop cancer sooner, especially if it is in a cell type that rapidly divides - aka increases the chances of acquiring more mutations because it has to keep dividing.

Finally, the title of this podcast/journal entry, was "How do we get cancer?", and I never even mentioned a single cancer-causing agent or carcinogen. The truth is, there is tons of these, and how they actually work would be another full podcast or article. The very brief answer using cigarettes as a well-characterized example, is that the smoke can damage lung cells by causing damage to your DNA. Basically these cause not only mutations/misspellings talked about earlier, but they can cut whole words out, or other words can be added where they shouldn't be, and this can all happen much more frequently than how the mutations naturally occur. Remember, though, it's WHERE these mutations and misspellings occur that matter the most, if you have them in the tumor suppressor genes, proto-oncogenes, or migration genes they can have a much worse effect.

So in the end, I've ended up ignoring tons of things from how the immune system helps prevent cancer to many other types of cancer-causing agents (radiation, sunlight, viruses), but I really do hope that I've helped you understand the basics of Cancer Biology. When I submit the written form of this, I'm gonna leave little notes on the side to point out any oversimplification, side notes, and/or my sources for what I've said/written. I plan on doing six of these podcasts in total; one per month from July 2017-January 2018. The current topics I'm planning on are: "Why isn't there a cure for cancer/New Therapies?" and "Why do we still use stem cells?" The future topics could vary quite a lot though, and although this one was more of a lesson or lecture, I believe the future ones will be more of an exploration so I can go on the journey with you guys and tell you what I figured out.

Honestly, I'm really only doing this to help you all be better informed; I know that sometimes science is poorly-communicated to people outside of the field and it makes it Really hard to understand. On that note, if you guys don't like this or appreciate this, I'll be happy to stop, and if there is anything you'd like me to improve on, just let me know! Also, if you guys have any questions on any topics you want me to try and cover (Vaccines, GMOs, global warming, etc.) I'll certainly do my best to be your scientist on-call and really take the journey with you guys.. I look forward to tackling some of these scientific problems!

So thank you all for listening/reading and I look forward to answering questions you guys have about anything I've said today of the above and looking forward to what you guys want to hear about next!