TELOMERASE DOES NOT CAUSE CANCER

One of the reasons I'm writing this book is to explain why public enthusiasm for pursuing telomere lengthening science and technology is very well-founded. That age reversal is not science fiction, but something we can really bring to fruition within our lifetimes. So it's important to address one of the biggest obstacles to that enthusiasm—the persistent rumor by some that telomerase induction, once achieved, would cause cancer.

In a way it's inevitable that such a rumor would come to exist, simply because of the relationship that modern culture has with science. For centuries, we've read literature that presents a cure for aging as far too good to be true, as some sort of "deal with the devil." From *The Picture of Dorian Gray* to *Tuck Everlasting* to even lighter fare like the film *Death Becomes Her*, age reversal in fiction virtually always comes with strings attached—strings so pernicious that the "moral" of these stories is invariably that extending life is a disastrously bad idea, and that those who choose to age and die will ultimately be happier.

The false idea that telomerase induction causes cancer fits that ancient narrative very nicely, so it's not surprising that it was the first explanation people grasped for as soon as there was the faintest suggestion that telomerase and cancer are part of the same picture.

I was there when that suggestion first took hold. When I led the research at Geron Corporation that discovered human telomerase, we took telomerase and we put it into regular human skin cells, where telomerase is not naturally expressed. And we were able to show that those cells did not age and that their health did not decline. But at the same time, we took what's called the antisense of telomerase–a complementary DNA strand that prevents any telomerase production–and we put that into cancer cells. And what we discovered was that the cancer cells died, essentially from accelerated aging. Better yet, the same treatment had no effect on normal cells.

Initially, it looked like we had a cure for cancer on our hands. And although curing cancer using telomerase inhibition hasn't turned out to be as straightforward as it initially seemed, telomerase inhibition is still a major target for fighting cancer, and telomerase inhibitors are currently in clinical trials. This discovery is the reason I was awarded second place for National Inventor of the Year in 1997: it appeared that my team had actually discovered a plausible cancer cure.

But those experiments also turned out to be the genesis of the rumor that telomerase causes cancer: some people read about them and leapt to the conclusion that if telomerase inhibition cures cancer, telomerase induction must cause it. It's not good logic; it's completely unscientific; but to some people it just felt like something that somehow must be true.

Everything else set aside, when asking the question of whether telomerase causes cancer, there is one element of the issue that everyone seems to overlook. That is, **we absolutely already know without a doubt that a *lack* of telomerase definitely causes cancer.** For every study that even suggests that telomerase might cause cancer, there are at least ten studies that show that the lack of telomerase really does cause cancer.

Doesn't that almost make the question "does telomerase cause cancer?" irrelevant? Even if telomerase did cause cancer, you either have telomerase turned on or you don't; there is no third

option. So now the pertinent question becomes not "does telomerase cause cancer?", but "does telomerase cause cancer more than the lack of telomerase does?"

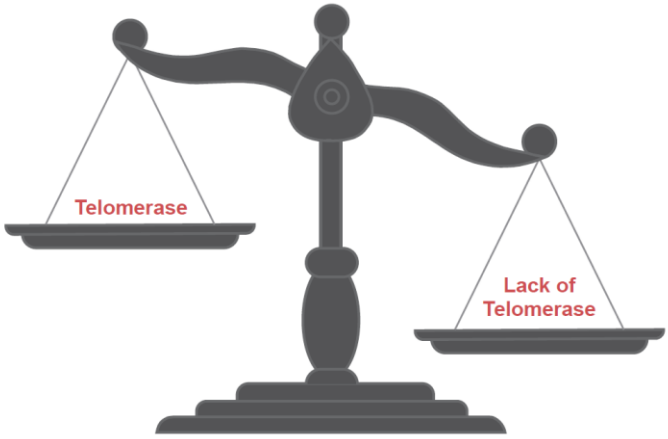
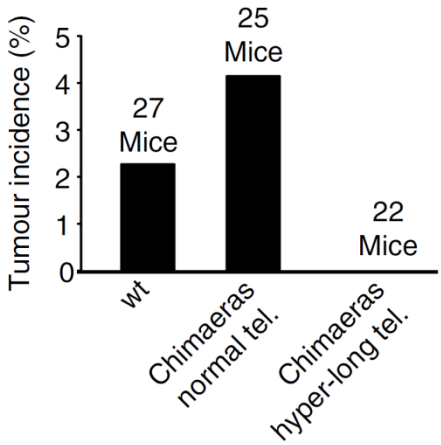


Figure 10-1: Scales showing for every study that suggests that telomerase might cause cancer, there are a hundred that show that the lack of telomerase does cause cancer.

And the answer is no, because telomerase doesn't cause cancer at all. Contrary to what some people might believe, there has never been a study in animals or humans that showed that induction of telomerase caused cancer; and many have tried. In fact, most such studies saw the exact opposite. Telomerase and long telomeres actually prevent cancer. See, for example, Varela E, *et al*. Nat Commun. 2016 Jun 2;7:11739, especially figure 6f (reproduced below).



Short Telomeres Cause Cancer

Most cancer does indeed consist of cells with telomerase turned on, but that's not because the cancer is caused by telomerase. In fact, it's exactly the other way around. The cancer comes before the telomerase is turned on. Cancer is defined as lack of growth control. This causes rapid cell division that allows telomeres to get really short; and the short telomeres dramatically increase the cells' mutation rate. A few of the cells then obtain a mutation (such as a chromosome rearrangement) that turns the telomerase gene on; and only those cells are able to divide past the Hayflick Limit. And in the end, what we are left with is a line of cancer cells producing telomerase.

In case I'm going too fast here, let me explain in more detail: one of the biggest causes of mutations in human cells, including chromosomal rearrangements, is short telomeres. Let's return again to the analogy of the shoelace. When the caps on our shoelaces get short, our shoelaces start to fall apart. The same thing is true in our chromosomes: when our telomeres get really short, our chromosomes start falling apart.

Seen under a microscope, this process of "falling apart" takes the form of chromosome rearrangements. A typical cancer cell with short telomeres often has hundreds of chromosome rearrangements, as well as tens of thousands of smaller mutations that cannot be visualized by light microscopy. A related phenomenon, called "chromothripsis," is also common when telomeres get really short—that is, when tens to hundreds of clustered DNA rearrangements suddenly result from a single dramatic event. This wreaks absolute havoc on the chromosomes; in fact, the word "chromothripsis" is derived from Greek affixes meaning "the shattering of the chromosome" because the genetic damage is so profound. With this many mutations occurring on a very frequent basis, the cancer cells can mutate to almost anything imaginable.

This is why most cancers come back after chemotherapy. Sure, chemotherapy will kill perhaps 99.9% of the cancer cells. But, because of short telomeres, a few almost always mutate to survive the chemotherapy, and the cancer comes back. And the mutations also lead to the expression of the telomerase gene, either by de-repressing the telomerase promoter or rearranging the DNA so that the telomerase gene is expressed from an entirely different promoter. Or, in some cases, the mutations lead to an alternative method for lengthening telomeres called the Alternative Lengthening of Telomeres (ALT) pathway. So much for killing cancer cells by letting their telomeres get short!

It is now well-established in the scientific literature that treating cancer by inhibition of telomerase to force cancer cells' telomeres to get critically short is leading to cancers returning with mutations to maintain their telomere lengths using the ALT pathway. And things still get worse! The short telomeres induce even further mutations that cause metastasis to occur allowing the cancer to spread throughout the body.

Let's not forget that our best defense against cancer is our immune system. That, too, will suffer from short telomeres, because for the immune system to fight the cancer, it needs to undergo a great deal of cell division, causing its telomeres to shorten. Very quickly, the telomeres in the immune cells become so short that they lose the ability to fight the cancer (or any other disease we might catch). This is called immune senescence.

Consider: Why is it that most cancer cells have critically short telomeres? It's very rare to find a cancer cell with long telomeres. The first thing that comes to mind is that the telomeres had to become critically short in the first place in order to allow the cells to mutate to become cancer cells. But, when cancers mutate further to induce telomerase, why is it that their telomeres don't get longer and longer?

This question always baffled me—until one day, it dawned on me that short telomeres actually give cancers a selective advantage to survive! Cancer cells live in a very "toxic" environment, in that our bodies' immune systems are constantly trying to kill them. Additionally, they have to develop means to get nourishment, either by inducing angiogenesis or modifying their nutritional needs to survive on less.

So like any organism in an extremely hostile and unstable environment, cancer cells need to adapt quickly, and they are able to adapt quickly because of the high mutation rates caused by short telomeres. When the immune system finds a way to fight a cancer, the existence of short telomeres means the cancer will more easily mutate to make itself resistant to the immune system. When a cancer finds that nourishment is not available, short telomeres help generate mutations in the biochemical pathways to allow nourishment in other ways. If telomeres were to get long in cancer cells the cancer would lose its selective advantage. And, so cancers survive better by keeping their telomeres short.

So, what's the bottom line here? Short telomeres are bad on many different levels. As I always say: "Bad Things Happen When Telomeres Get Short!"

Long Telomeres Help Fight Cancer

Though I can't imagine how telomerase could actually be the cause of cancer, it certainly is possible that telomerase could cause a very small new cancer to become healthier. That's because just like any cell, a cancer cell will be healthier if it is not rapidly approaching the Hayflick Limit. But sufficiently long telomeres are only one of many things that make all our cells (including cancer cells) healthier. Another simple example would be a healthy diet. And while starving ourselves half to death would be an effective way to make our cancer cells less healthy, we'd hardly consider it a reasonable therapy. Our bodies need to be as strong as possible to give them a shot at beating cancer.

Along the same lines, something that is often overlooked when accusing telomerase of helping cancer along is that telomerase will also strengthen our immune system by lengthening the telomeres in our immune cells, increasing the ability of our immune system to destroy cancer cells.

If our cancer cells were the only cells in our body that expressed telomerase, that would be a disaster. But, actually, that is exactly the situation we already face. Every time a cancer gets big enough to even detect in a person, past their evolutionary optimal child-raising years, it has already undergone enough cell division to cause its telomeres to get so short that the cancer should have already succumbed to senescence. But it hasn't, because it has mutated to maintain its telomere lengths, either by telomerase induction or by the ALT pathway.

Meanwhile, what *has* begun to senesce—to die of old age—is our own immune system. And so, the struggle between cancer and our immune system ends up being like two armies fighting where only one army has weapons. If we were to induce telomerase in every cell in the body, it would arm the immune system as well, giving it a fighting chance to defeat the cancer. Concerns that it would also arm the cancer are somewhat irrelevant, given that the cancer is already armed. You can't induce telomerase in a cancer cell any more than you can turn on the lights in a room where the lights are already on.

What you can do, is give the immune system a fighting chance against the cancer. And we know that when the immune system isn't suffering from senescence, it fights very well indeed. That's the reason that it's comparatively very rare for people to die of cancer in their twenties and thirties.

The GWAS Studies

As I said before, for every study that suggests that telomerase might cause cancer, there are at least ten that show that the lack of telomerase really does cause cancer. My first book, published in 2014, examined many of the studies that existed at the time, finding their consensus to be that cancers are caused by short telomeres, not long ones.

Shortly after that book's publication, there were seven studies, published since the beginning of 2015, which examined genetic variants that are correlated with long telomeres. These studies, called Genomewide Association Studies ("GWAS"), discovered that eight or nine genetic variations which correlate with long telomeres also correlate with an increased risk of cancer.

Naturally, proponents of the "telomerase causes cancer" model have seized on these studies as support for their argument, but a careful examination of the studies shows that they don't support that argument at all.

First, the authors of the studies have never been able to show that the genetic variants themselves didn't cause cancer by non-telomere-related events in the cell. These genetic variations, called Single Nucleotide Polymorphisms (SNPs), are well known for pleiotropy (where a gene has more than one genetic function). In fact, the authors of all the GWAS studies even cautioned readers that pleiotropy by SNPs is very common and couldn't be ruled out. In other words, the studies may be finding that there are a few genes in our bodies that, in some circumstances, can lengthen telomeres; and in other circumstances, can cause cancer; and that the two functions of those genes have little to do with one another. It's unclear.

Second, the studies weren't able to suggest a causal effect, and surely we're all aware by now that correlation is not causation. A finding that a number of SNPs are correlated with both long telomeres and cancer doesn't imply that long telomeres cause cancer—not any more than a finding that bad weather is correlated with both car accidents and flooding implies that car accidents cause flooding.

Third, the authors of the GWAS studies never actually measured telomere lengths! They simply inferred that telomeres must be long because of the presence of SNPs that had previously shown a correlation with long telomeres. Given our incomplete understanding of those gene variants, I'm reluctant to give much weight to these studies.

Fortunately, during the same time period that these GWAS studies were published, there were 42 other published studies that actually did measure telomere lengths, and every one of these studies showed that *short* telomeres correlated with an increased risk of cancer and that long telomeres did not.

So what we have is a situation where proponents of the "telomerase causes cancer" model emphasized seven studies that argued that cancer might be more prevalent in cells with long telomeres, based on SNPs that had been correlated with long telomeres—while somehow managing to "overlook" 42 studies that measured telomeres and correlated short telomere length directly with cancer.

Telomere Length and Cancer Risk

- Meta-Analysis 2015-2017
- 13 Studies looked at telomere length and risk of cancer by GWAS
- 56 Studies looked at telomere length and risk of cancer by Measuring Telomere Lengths

Cancer Risk	GWAS	Measured Telomeres
Long telomeres	7	4
Short telomeres	1	42
No association	5	9
Both		1
	13	56

Full text of these studies can be found at www.sierrasci.com/papers

Why the emphasis on the seven questionable outliers? Well, the truth of the matter is: shocking and alarmist findings always get more press than solid science. There could be years of scientific consensus establishing beyond any real doubt that jellybeans do not cause cancer, but if one outlying study erroneously finds that green jellybeans cause cancer, I think we all know which one study will get a mountain of press. It seems that in recent years, telomere biology has fallen prey to this very phenomenon.

If you want the truth about science, don't rely on press releases and news reports. It may sound cynical, but it's my experience that time and time again they will misinform you: sensationalism means clicks, and clicks mean ad revenue, so sensationalism is what you get. If the truth is important to you, you'll need to review the scientific peer-reviewed research studies that are available to everyone in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/).

The Evolutionary Basis of Cancer

So, why do our telomeres shorten? That sounds like an awful thing to have happen to us if we think we should have evolved ways to live healthier longer, not to die sooner.

A popular hypothesis that's been kicked around by some scientists over the last few decades is that telomere shortening is actually an anti-cancer mechanism. The thought is that perhaps our telomeres shorten specifically so that cancers can't become particularly dangerous, and that aging itself might just be an unfortunate side effect of cancer prevention. But, hopefully, after reading everything I just said about telomeres and cancer you know this doesn't make any sense. Allowing telomeres to shorten is a very ineffective way to fight cancer. People in their evolutionary optimal child-raising years still have telomeres more than long enough to allow their cancers to kill them many times over without ever needing telomerase to lengthen the telomeres.

To answer the question "why do telomeres shorten," we need to understand evolution more carefully. Evolution doesn't strive to make us live longer and healthier. It strives to increase the chances that we pass on our genes, while simultaneously shuffling our genes to ensure that we can

always survive a rapidly-changing environment. Shuffling of our genes is much more efficient when offspring breed among each other instead of breeding with their elders. Evolution also strives to keep the offspring alive and healthy so that they will be more likely to breed and produce more offspring.

But, after they have raised their offspring, the parents of those offspring are just in the way. They have become competition with their offspring for food, mates, and in the case of modern humans, jobs. So, for a species to be successful in a rapidly-changing environment, it is always best to "knock off" the old, who have become a burden to the species—nothing more than excess baggage. And so it's easy to see how telomere shortening isn't an anti-cancer mechanism at all; it is a pro-death mechanism to eliminate that excess baggage.

The bottom line is that there is no evolutionary advantage to living longer than it takes to raise our young. So, in the case of humans, other primates, dogs, cats, horses, sheep, pig, and deer, these animals all evolved a mechanism of eliminating the old called telomere shortening.

Rodents, such as mice, evolved an entirely different mechanism. They actually have no telomere shortening. And, they have telomerase produced in all their cells. Rodents typically die from declining health due to oxidative stress and mitochondrial dysfunction. It's almost as if they are born with a person inside them blasting a machine gun in all different directions until they succumb to all the bullet holes.

And, then, there are animals on this planet that have no detectable aging—species that survived despite lacking a clear mechanism for knocking off the old. Most often, these animals are found in particularly stable environments; they include lobsters, tortoises, clams, and whales, to name a few. All these animals have been shown to have telomerase produced in all their cells, and they have no telomere shortening. And, they rarely get cancer and other diseases.

So, how long do these animals live? We still don't know. Most animals don't have something like rings on a tree that we can count. The only way to tell, in most cases, is to be there when the animal is born, put it in a cage or aquarium, and then watch it until it dies.

People never really thought of doing such a thing until the time of Darwin, but now people have been watching some of these animals for more than 150 years and still they see no detectable aging. It's not typically possible to determine these species' age, but there's one interesting exception: clams. Clams grow a little bit like trees, where they accumulate a new "stripe" each year, like a tree's rings. Clams have been now found with over five hundred stripes, suggesting that Columbus may have sailed over claims that are still alive today.

It would seem, then, that it is not inevitable that we must decline and die. Some may claim that agelessness is unnatural, but as we can observe, it's perfectly natural, in that many animals already do not have an aging process and rarely get cancer. And soon, we will have the opportunity to join them.

Closing Thoughts on Cancer

Finally, informed readers might have noticed that I haven't mentioned anything about potential secondary activities of telomerase, often referred to as "moonlighting". In the past, several published papers have suggested that the supposed cancer-causing qualities of telomerase

might be due to “extracurricular” activities of telomerase besides lengthening telomeres. But there haven’t been any such publications in over ten years, and none of the older studies have been supported by any subsequent studies. Until someone discovers some activity of telomerase that could theoretically increase the risk of cancer, it seems pointless to speculate on whether “moonlighting telomerase” is a phenomenon that even exists.

To conclude my discussion of cancer: in my opinion, the best way to fight cancer is not to inhibit telomerase to cause telomeres to get short, but rather to induce telomerase to lengthen telomeres to decrease mutation rates and strengthen the immune system. If we could combine this treatment with a theoretical telomerase poison that kills telomerase-positive cells without allowing the telomeres in other cells to shorten, that would be even better, as long as the patient was not treated with both at the same time.

For those of us fortunate enough not to have cancer, the best way to prevent cancer is to induce telomerase to prevent the large number of mutations caused by short telomeres that cause cancer. In other words, the bulk of the evidence suggests that telomerase induction will not only *not* cause cancer, but will do the exact opposite: help prevent cancer. Bottom line: if you choose not to induce telomerase to protect yourself from getting cancer, you are probably only increasing your chances that you will get cancer and die from it.

If you still believe that telomerase causes cancer, by all means please write to me and explain why. I am at a loss for any reasons why it could be true. I can be reached through my website at www.sierrasci.com/contact.