

## **From\_Teenage\_to\_Old\_Age\_How\_Cancer\_Develops\_Over\_Time\_English\_mp4\_**

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[00:00:20.12] CHRISTINA HUANG: Hi. Welcome to our lesson on cancer here at the Broad Institute of MIT and Harvard. My name is Tina, and I'm a scientist here at the cancer program.

[00:00:29.46] ALICE BERGER: My name is Alice, and I'm one of Tina's colleagues here in the cancer program.

[00:00:33.30] CHRISTINA HUANG: In today's lesson, we'll be talking about cancer. But first, let's consider an analogy that demonstrates how cancer develops over time due to the accumulation of mutations.

[00:00:43.70] LUC DE WAAL: So, I guess I'll see you Friday--

[00:00:46.35] CHRISTINA HUANG: Let's meet my friend Luc. Luc's talking to its friend on his cell phone.

[00:00:50.31] LUC DE WAAL: All right. Bye. [PLOP] Oh, no.

[00:00:56.20] CHRISTINA HUANG: Luc dropped his phone when he was sitting on the couch, but luckily it still works. Unluckily, however, a few months later he manages to drop his phone again while he is studying for his biology class. And later, he drops it again while talking to his friend Laura.

[00:01:11.73] Another few months pass, and Luc has a particularly unlucky day where he drops his phone twice outside. The second time it falls that day, it breaks for good.

[00:01:21.81] LUC DE WAAL: Hello? Hello?

[00:01:24.79] CHRISTINA HUANG: What we want you to do now is to turn to your classmates to answer a couple questions, and then when we come back, we'll tell you a bit more about how this relates to cancer.

[00:00:00.00]

[00:01:56.45] So what you just saw earlier was an analogy where the cell phone is like a cell, and a broken cellphone is like a cell that's become cancerous. And, as you saw with the cell phone, it had to be dropped many, many times before it actually broke. And this is very similar to a cell where lots of mutations in DNA have to accumulate before a cell can actually become cancerous.

[00:02:18.74] So that's why cancer is a disease of old age. So, now we know that mutations cause cancer. But what is it that causes mutation? Take the time to talk to

your classmates about it for a couple minutes, and then I'll see you when we get back.

[00:02:43.92] Welcome back. By now you should have created a list of the various things that might cause cancer, which probably includes UV light, x-rays, and cigarette smoke. How do these cause cancer? They do so by damaging your DNA. When DNA is damaged, two things can occur.

[00:03:01.31] One, when the cell tries to repair itself, it inserts the right nucleotide, and the DNA is properly repaired. Two, when the cell tries to repair itself, it inserts the wrong nucleotide, and a mutation occurs.

[00:03:15.81] Now your teacher is going to lead you in a game that demonstrates how mutations occur over time. And when we come back, my colleague Alice will be here to discuss with you about the results of that game.

[00:03:38.51] ALICE BERGER: Welcome back. As you just saw in your mutation matt activity, when you acquire a certain set of mutations in a certain set of genes, cancer can occur. And you can start to understand how cancer is a set of diseases that is similar, but they can all be a little bit different, depending on which sets of mutations are acquired.

[00:03:57.96] And those mutations affect the genes in your cells. So if these genes are present in all of our cells and all of our bodies, what are they doing normally? Well, many of the genes that are mutated in cancer have normal function involved in processes such as cell division or cell death. And so, why would you need these genes normally to regulate things like cell division?

[00:04:20.80] Well, you can imagine there are lots of times when you would want to control whether a cell divides or not. For example, what if you had a cut? You would want your skin cells to grow and divide and cover up that wound, and then eventually you would want them to stop.

[00:04:36.97] Another way to think about this is as an analogy with a steam engine train. In a steam engine, you need some people to shovel the coal to provide the fuel to make the train go forward. And you need other people to pull the brakes that make the train stop. There are lots of things that can go wrong that might make the train go too fast or too slow.

[00:04:55.74] So now we're going to have an activity where you can think about those things go wrong and predict what will happen next, and I'll see you when you get back.

[00:00:00.00]

[00:05:18.12] Welcome back. In the last activity, you looked at all the different things that could go wrong with a train. And you saw that sometimes these

problems were caused by losing a function of a train worker, and sometimes they were caused by too much of a certain activity, or even a new function.

[00:05:39.98] And in biology, we refer to these two types of mutations as loss-of-function or gain-of-function mutations. In the train analogy, the brake pullers represent tumor suppressor genes, which are genes that normally inhibit cell division, and the coal shovelers represent oncogenes, which are genes that normally promote cell division.

[00:06:02.30] In cancer, sometimes we find loss-of-function mutations in tumor suppressor genes. So these loss-of-function mutations block the function of those genes that normally act to stop cell division, and therefore you get uncontrolled cell division, and eventually a tumor.

[00:06:19.17] And similarly, we see in cancer gain-of-function mutations of oncogenes. So these oncogenes that normally promote cell division become hyperactive, and therefore, also cause uncontrolled cell division. In the next activity, we're going to revisit the train analogy, and ask you to focus on the following things.

[00:06:40.25] Did both brake pullers need to be mutated in order to see the effect that you saw? And did both coal shovelers need to be mutated in order to see the effect that you saw? Answer those questions, and then I'll see when you get back.

[00:07:04.33] Welcome back. In the last activity, you saw how mutation of only one of the coal shovelers could cause the train to go out of control, but mutation of both of the brake pullers was needed in order to make the train go out of control. So how come we had two versions of each of these people anyway?

[00:07:21.28] Well, they were meant to represent the two versions of every gene that you inherit from your parents-- one version from your mother, the maternal version-- and one version from your father, the paternal version. So that mutation matt that we looked at earlier was actually an over-simplification, because it should have had twice as many squares if we had represented both versions of each gene.

[00:07:43.12] Also, until now, we've been talking about mutations that you acquire during your lifetime. But you can also inherit certain mutations that might predispose you to develop cancer. Let's think about this in the context of tumor suppressor genes which, if you remember, are like the brake pullers in the train analogy. So you need to lose both copies of a tumor suppressor gene in order to get cancer.

[00:08:06.69] In some cases, you might inherit one mutated version of that tumor suppressor gene, and then you could acquire a mutation in the other version of the gene and develop cancer. And so you'd actually be a bit more predisposed to cancer than someone who didn't inherit one of those mutations.

[00:08:24.80] You may actually know a family with an inherited cancer predisposition, if you know a family where multiple people have developed the same type of cancer at an unusually young age. So, for the next activity, we'd like you to analyze the number of mutations found in different genes in a patient with an inherited cancer predisposition-- versus a patient who doesn't have one-- in different cell types in the body.

[00:08:48.13] We'll give you a minute to do that and then I'll see when you get back.

[00:09:01.24] Welcome back. As you saw the last activity, someone with an inherited predisposition to cancer has one mutated form of a gene and one non-mutated form of a gene in all the cells in their body. But in the cancer cells, they've acquired an additional mutation, so that now in the cancer cells they have two mutated versions of that gene in the cancer cell.

[00:09:23.66] Someone without an inherited predisposition to cancer has two non-mutated copies of the gene in all of their cells, and in their cancer cells, they still have two mutated versions of that gene, which they've acquired over their lifetime.

[00:09:37.02] Now, on the mutation matt, we were talking about skin cancer, and in the last activity, we were talking about retinoblastoma-- a tumor of the retina in the eye. Many different tissues can develop cancer, and each of these tissues are exposed to different chemicals that can cause mutations in your DNA.

[00:09:52.65] For example, if you smoke, smoking enters your lungs, and the smoking cause mutations in your lung cell DNA, eventually resulting in lung cancer. When you eat, different chemicals in the foods that you eat can sometimes cause mutations in cells in your digestive system, possibly leading to cancer in that tissue.

[00:10:09.66] Also, when you have sun exposure, harmful UV radiation from the sun can induce mutations in your skin cells, eventually leading to skin cancer. Because your sun exposure, whether you smoke or not, and what foods that you eat are all lifestyle decisions, the choices you make can actually impact your risk of cancer.

[00:10:26.98] CHRISTINA HUANG: Remember my friend Luc? Well, here's his phone, and it's broken.

[00:10:30.53] ALICE BERGER: That's right. I wonder what Luc could have done to help to prevent his phone from breaking. He could have made some choices such as putting a case on his phone, or not putting it so close to the edge of the table. We here at the Broad are studying cancer to try to figure out what causes cancer, so we can help to better prevent it.

[00:10:47.71] Thank you for joining us on this lesson.

[00:10:49.53] CHRISTINA HUANG: We hope you enjoyed it.

[00:11:01.53] PROFESSOR ROKOP: Hi. Thanks for considering using our lesson on how cancer develops over time due to an accumulation of mutations. This lesson was developed here at the Broad Institute of MIT and Harvard. My name is Megan Rokop, and I'm the Director of the Educational Outreach Program here at the Broad.

[00:11:17.41] Let me tell you a little bit about our lesson. For prerequisite knowledge for our lesson, there's not much prerequisite knowledge required. It is helpful if the students are familiar with DNA, and the fact that it is the genetic information, and made up of four bases, A, T, G and C.

[00:11:34.15] It's also helpful if the students know what a mutation is-- that is, that there's a different letter-- A, T, G or C-- in this place where a different letter normally is. In terms of materials required for this lesson, the only materials necessary are the worksheets and the slides that we provide.

[00:11:51.06] I'm going to go through each segment, and tell you what happens in each segment, and what the students do in the activity between segments. In segment number one, we introduce our lesson by introducing an analogy. The analogy is that a cell phone is dropped over time. The first four times a cellphone drops, it doesn't break, but the fifth time it's dropped, it breaks.

[00:12:11.98] We ask the students to answer a few questions about this that lead us into segment two, where we discuss how this is an analogy for cancer developing over time. The analogy is that the phone is a cell, and that dropping the phone is like DNA experiencing damage. The cell accumulates damage over time, and that leads to it being cancerous.

[00:12:33.21] At the end of segment two, we ask the students to make a list of different things that they can think of that might cause mutations. When we come back in segment three, we give the students a list of examples of things that cause mutations, such as UV from the sun, or cigarette smoke, or chemicals in the food that you eat.

[00:12:52.59] We show a students a picture of DNA that's been damaged, so that you can see what it looks like for DNA to be damaged. And then we talk about how damaged DNA is repaired in the cell. Sometimes those repairs lead to the correct base-- A, T, G or C-- being put back in. But sometimes the incorrect base is put back in, and this causes a mutation.

[00:13:15.10] At the end of segment three, we introduce a game or activity that the teacher will lead the students in. In this activity, the students receive a mutation matt. It's kind of like a bingo board, and each square has a different gene name.

[00:13:28.54] The teacher draws a series of gene names from a hat. Each draw represents a few years in the life of the cell that is represented by the mutation matt. The students cover the gene names with bingo chips as these genes accumulate mutations.

[00:13:46.25] By the end of the game, some of the mutation mats have experienced a set of mutations that lead that cell to become cancerous, and others haven't. The students discuss how many different cells in the activity have accumulated the set of mutations that leads to development of cancer.

[00:14:03.32] When we come back in segment four, we talk about why we chose the genes we did for the mutation mat. These genes are genes in the cells that normally function to control cell growth and division. We have genes in all of our cells that either normally promote cell division or normally inhibit cell division.

[00:14:23.28] We talk about how these genes are tumor suppressor genes-- genes that normally inhibit cell division-- and oncogenes-- genes that normally promote cell division. We tell the students to think about these genes in another analogy where we used a train with a steam engine.

[00:14:39.58] In this analogy, we have people who shovel coal into the engine, and the coal shovelers are like the oncogene. We have people who pull on the brakes in the train, and they're like the tumor suppressors.

[00:14:51.55] So what we do at the end of segment four is we give the students a worksheet with a list of different train scenarios where different things have gone wrong with the brake pullers and the coal shovelers. We ask the students to predict what the effect on the train is in terms of the train running out of control.

[00:15:10.67] When we come back in segment five, we talk about how the worksheet that the students just did had two different types of mutations-- loss-of-function mutations, where the genes just stopped working, or gain-of-function mutations, where the genes either worked too much or acquired a new function.

[00:15:28.50] We then ask the students to go back to their train worksheet and to analyze whether-- for the coal shovelers or for the brake pullers-- whether both coal shovelers had to be mutated for the train to go out of control, or just one, and whether both brake pullers had to be mutated for the train to go out of control, or just one.

[00:15:49.48] When we come back in segment six, we talk about how, when loss-of-function mutations occur in tumor suppressor genes, both versions of the tumor suppressor gene need to be mutated to cause cancer. The reason we had two coal shovelers and two brake pullers on our train was that we were representing the fact that each gene in our cells, there's two different versions-- the maternal version from the mom, and the paternal version from the dad.

[00:16:16.19] With oncogenes, only one of those versions has to be mutated. A gain-of-function mutation occurs to lead to cancer. But with tumor suppressor genes, both the maternal and paternal versions need to be mutated.

[00:16:29.32] We talk about how mutations in, for instance, a tumor suppressor gene can accumulate over time. But a person can actually be predisposed to cancer if they inherit one version of the tumor suppressor gene that is mutated from one of their two parents. This means they have fewer mutations that they need to accumulate over time in order to lead to cancer.

[00:16:52.43] We ask the students after segment six to compare the different versions of the tumor suppressor genes in a patient's DNA-- one patient who was predisposed to cancer, and thus inherited one mutation from one of their parents, and then the mutations in another patient's DNA, where that patient was not predisposed to cancer, but developed it over time.

[00:17:15.72] When we come back in segment seven, we see how the patient who was predisposed to cancer had a mutated version of the tumor suppressor gene in all of the cells in their body. But in the tumor cells, they then accumulated a mutation in the other version such that that cell led to being cancerous.

[00:17:34.47] However, in the person not predisposed to the cancer, most of the cells in that person's body had two unmutated forms of the tumor suppressor gene. And then the cell that became cancerous accumulated, over time, mutations in both of the versions of the tumor suppressor gene.

[00:17:51.89] We talk about how families where the members of family are predisposed to cancer are families in which the same kind of cancer occurs over and over again in the different members of the family, and those family members get the cancer very young.

[00:18:09.04] We end by talking about a review of the activities we've done. For instance, the mutation matt activity, which had to do with skin cancer, and the comparing the patient who was predisposed to cancer to the one who wasn't, which had to do with retinoblastoma, or cancer of the retina of the eye.

[00:18:27.03] We talk about how cancer can develop in many different tissues, and that's because many different tissues are exposed to different chemicals that may cause mutations in the DNA of different cell types. So, for instance, sun exposure makes UV rays exposed to the DNA of skin cells, and that's why sun exposure can lead to skin cancer.

[00:18:48.58] But the chemicals in the food we eat encounter the lining of our intestine in our digestive system. So those, for instance, could lead to colon cancer. In contrast, when you smoke, the mutations in cigarette smoke affect your lung cells, which is why that can lead to lung cancer.

[00:19:04.88] So, we end by talking about how-- because smoking and sun exposure and the foods we eat are lifestyle choices-- it's possible to make lifestyle choices that decrease our risk for cancer. And we talk about how, here at the Broad, we're interested in trying to figure out the different causes of cancer, so that we can learn

not only how to cure different kinds of cancers and treat different kinds of cancers, but also how to prevent different kinds of cancers.

[00:19:30.71] Thank you for considering our lesson, and I hope you enjoyed this teacher segment.