

## MITOCW | watch?v=b\_lgH\_ZnCmg

---

The following content is provided under a Creative Commons license. Your support will help MIT OpenCourseWare continue to offer high quality educational resources for free. To make a donation or view additional materials from hundreds of MIT courses, visit MIT OpenCourseWare at [ocw.mit.edu](http://ocw.mit.edu).

**TYLER JACKS:** OK. So now we're going to change gears entirely, and talk about cancer. And to put you in the mood to talk about cancer, I'm going to show you a video, which we actually produced last year for the American Association for Cancer Research annual meeting, to open up that meeting, actually. Hopefully, there's sound. Guys, upstairs?

[VIDEO PLAYBACK]

[END PLAYBACK]

**TYLER JACKS:** Hopefully, you're inspired. That video is on YouTube if you want to watch it again. It's got to 15,000 hits. It's not exactly viral, but still pretty good, pretty good for a cancer research video. And the video really was to kind of get people excited about both the progress that's been made and the opportunity that exists. But also some of the great challenges that we're referred to in some of those facts and figures that you saw there.

So I want to review some of that with you, and give you a sense of what we're doing to improve our progress, accelerate our progress. And the bottom line is I'm actually extremely excited about the potential that we'll have over the next decade or two in really changing the course of some of those numbers that you saw there. But just to remind you of the severity of the problem, when we consider the statistics regarding cancer in the United States, in the United States over the next year, there'll be about 1.4 million new cases in the United States.

That does not include common forms of skin cancer-- squamous cell skin cancer, basal cell skin cancer contribute another million cases. So it's a very, very common disease, very commonly diagnosed in this country, and indeed, around the world. Again, just considering the next year, it's estimated that there will be about 560,000 deaths in the United States due to cancer, and about 8 million in the world. And you might have seen the statistic that more people die in the world of cancer per year than of malaria, TB, or HIV aids combined. So very, very common, very, very deadly disease.

In this country, the lifetime risk of developing cancer is 1 in 2 for men, 1 in 3 for women, based on current statistics. Again, hopefully by the time you guys are old and cancer typically is a disease of older people, these statistics will change. But that's what they are now. So if they

don't change, then a large number of you sitting here will experience this diagnosis. And by current statistics, 1 in 4 deaths are due to cancer.

Cancer has recently bypassed cardiovascular disease as the leading cause of death in the United States. Cardiovascular disease rates have dropped precipitously. Cancer rates have dropped less significantly, although they are coming down. Also, the population is aging. And cancer tends to be a disease of older people. So the demographics also increase the numbers of people who are dying from this disease. So a major problem.

But also think of it as a major opportunity to do something really important if you choose to get into this field. So cancer, I think, is familiar to everybody on one level or another, but you might not have seen the disease up close. I hope that you haven't. But I want to teach you a little bit about what it looks like, and really what are some of the fundamental definitions.

So lung cancer, a very commonly diagnosed cancer in this country-- we'll talk more about it in a minute-- is diagnosed either by a chest x-ray following symptoms, and you can see perhaps, although the light isn't great here, that there's a dark mass right here. And this dark mass indicates the presence of a tumor. A more refined diagnosis can be done by basically serial x-rays, computed tomography. And you can see this very clearly defined mass growing in the lung of the individual.

Cancer is an accumulation of cells, an abnormal number of cells within a tissue. And you can see that solid tumor here and here. You can also see cancers in the blood. Again, an abnormal number of cells within the blood, a leukemia. This is a normal blood smear. Here are red blood cells. And here is a normal number of white blood cells. These might be B-cells. These might be neutrophils. And you can see an accumulation of these nucleated white blood cells in this leukemic patient. Thousands, hundreds of thousands more of these cells than should be present within this blood sample.

This is colon cancer. Colon cancer, as you probably know, can be detected by colonoscopy, a very important diagnostic test, preventative test. And we can actually see the lining of the colon. And this is a normal section of colonic epithelium. And here is a tumor developing. It's called a polyp. This is an early stage, precancerous tumor. We'll talk more about the details of that in a second.

If this is diagnosed during endoscopy, they're actually removed right during the procedure. And this is very important to prevent those tumors from progressing further into true cancer.

And actually, colon cancer rates have dropped significantly because of this test. When these lesions are discovered, they are removed. And therefore, they can't progress into true colon cancer.

However, sometimes you see this. And this is a tumor that has progressed further. It's divided more. It's taken on additional abnormal properties and actually moved through the wall of the colon and is beginning to spread throughout the body. This is true cancer and much, much harder to treat. Not impossible, but much harder to treat.

When this is discovered, you can't just remove the specific lesion. You have to have surgery. And a section of the colon is removed to take out the tumor in the hope that that will get rid of the disease entirely. But the concern is, in this situation, that the diseased cells might have moved out into the body in the process of metastasis, which will make the disease much more difficult to treat.

OK. So I've given you some terminology there. Let me just explain some of it in greater detail. Actually, before I do that, let me show you one more, a couple of slides. So as indicated on that slide, cancer develops in stages from normal cells through the development of a benign, precancerous lesion, finally to the development of true cancer. And we can depict that graphically, as shown here.

This is a normal tissue. Here are normal cells. These might be epithelial cells lining the intestine. Those cells sit on top of a basement membrane made of extracellular matrix proteins, which provide them structure and some function. There might be other cells present in this region, stem cells or progenitor cells, which will replenish those differentiated cells as they are sloughed off and die.

These cells can acquire alterations-- and we'll discuss this in great detail today and next time-- alterations in their genes, which allow those cells to do things they shouldn't do, namely to proliferate abnormally. So rather than having a single line of cells, we now have a little clump of cells. These cells might look identical to their neighbors, but there are too many of them. This is a process we call hyperplasia, too many cells, too much growth.

Within this collection of cells, additional alterations may take place that allow those cells to divide more rapidly and to do even more abnormal things, to pile up on one or another, which they shouldn't normally do. This is the development of one of those early stage tumors. I showed you a polyp in the colon. That's a stage of cancer, in the case of colon cancer, called

an adenoma. That's a benign tumor. It's not yet cancer. It's actually not yet life threatening. But it's detectable because it's a mass of cells that shouldn't be there.

Within that collection of cells, still further alterations can take place. And now the cells do additional things that are wrong and potentially dangerous. One, they're recruiting a blood supply. They're recruiting blood vessels into the tumor to nourish the tumor and bring factors that the tumor cells need for their survival.

In addition, the cells are starting to degrade that extracellular matrix. They're starting to acquire the ability to move away from their normal site. Most cells in your body know where they're supposed to be, and they stay there. Cancer cells acquire the ability to leave their primary site and to disseminate throughout the body, creating secondary tumors. This happens when the cells access the blood vessels. They can then travel within the blood system and then take up residence in some secondary site. And this we call metastasis.

Metastatic tumors are tumors that are derived from the primary cancer-- and this is true cancer here-- derived from the primary cancer, that have now created a secondary tumor somewhere else. And this is actually the most lethal phase of cancer. Of the 560 cancer-- 560,000 cancer deaths that will occur in this country this year, 500,000 of them are due to this phase of the disease. It's actually not a phase that we understand terribly well today, but clearly a very important one.

So cancer arises from normal cells through the sequential acquisition of alterations that allow those cells to do things they should not normally do, including invade and metastasize. This is what it looks like in real life. This is a tumor. It's actually a tumor from a mouse created in my lab. It's lung cancer. This lacy appearance is the normal lung epithelium. There's a lot of air spaces in the lung to allow you to get gas exchange in the lung.

And you can see in this region right here, there's a bit of a thickening of those epithelial structures. Too many cells, that's this area we call hyperplasia. Over time, these will give way to solid growths. The cells within those solid growths look pretty normal. And you might be able to see that here. The cells are pretty well organized. They are all lined up. There's just too many of them. That's a benign tumor, an adenoma.

Over time, these will give rise to true cancers, carcinomas. And these have the ability to spread locally and throughout the body. In addition, the cells look even more abnormal. They

don't look like the cells that gave rise to them. OK. Now let me give you some more details of the terminology that I've just been using.

Hyperplasia is increased cell number. But the architecture of the cells is otherwise normal. They look like normal cells. If progression occurs, a benign tumor might arise. This is not yet cancer. These tumors are so-called not aggressive. They basically stay where they started. They don't destroy the local tissue. And they don't leave the site.

And if they are detected, for example in a colonoscopy, they can be removed. If they're detected in the lung when they're at this stage, they can be removed surgically and the patient will be fine. However, they can progress into a malignant tumor. And this is where we use the term cancer. Cancer actually refers not to just any tumor, but a malignant tumor. And these, by contrast, are aggressive.

The cells are dividing more rapidly. They're also causing changes within the local tissue such that they're locally destructive to the local tissue. And they have the potential to spread, to get outside of their local area, access the blood vessels, and move to a distant site. And that leads to this final phase of metastasis, which is the tumor growing at a distant site. And that can be one site or it can be many sites. And again, it's the combined effects of the metastatic tumors that tends to kill cancer patients.

Now cancers can arise in virtually all organs, all tissues. Cancer is an umbrella term that actually refers to many different diseases of abnormal growth. The most common tumors in humans affect epithelial tissues, epithelial tissues. And these epithelial tissues will give rise to a cancer type called carcinomas. Carcinomas are cancers of epithelial tissues. Breast cancer, lung cancer pancreas cancer-- these are all cancers of epithelial tissues. The precursor lesions are called adenomas, in many cases. And these are benign.

We can also have cancers of connective tissues, and these are called, collectively, sarcomas, sarcomas. Muscle tumors, myosarcomas. Fibroblast derived tumors, fibrosarcomas. Cartilage derived tumors, these tumors are rarer in humans, but they occur. And when they occur, they can be quite problematic, as well. And they go through similar stages of progression, as I've been describing for the other tumor types.

And we can have tumors of blood cells, leukemias, too many cells in the blood. And I showed you a blood smear of a leukemic patient. The blood smear indicates that there are too many cells circulating. That contrasts to lymphomas, which is also a blood cell tumor. But here the

tumor cells are confined to lymph organs, like the thymus or the spleen or lymph nodes. So there actually aren't too many cells circulating, but there are too many of these cells in these structures, which likewise can cause problems within those local structures, and surrounding tissues as well.

OK. So some terminology. Cancers affect all tissues, or virtually all tissues. There are probably 200, 250 different types of cancer when we think about all the different cell types in your body that can undergo these changes and result in one or another type of cancer. All right. So cancers arise from normal cells. They develop in stages. What causes them to change over time? What gives them the ability to divide inappropriately, to grow abnormally?

The answer to this question is that alterations take place in the DNA of the developing cancer cells. And in this respect, cancer is a genetic disease. And I'm going to use this term in quotes because when we talk about a genetic disease, we tend to talk about inherited diseases. You inherit a disease allele from one of your parents. You develop a disease.

In this case, cancer can arise as a consequence of an inherited mutation. We'll talk about that in a subsequent lecture. But what I'm referring to here is genetic alterations that take place within you, within your cells. And this accumulates over time, over decades in some cases, and allows the cells to progress through these various stages.

The case that cancer develops through the acquisition of mutations in genes has been building for about a century. We've been suspecting that cancer was a genetic disease for a very long time. And now we know it's true because we've seen the alterations in the genes of cancer cells. And we'll come to those specific alterations in subsequent lectures. But I want to give you the background that led us there.

The first and the oldest was the observation going back almost 100 years that cancer cells have abnormal number and structure of chromosomes. As you know, your cells have 46 chromosomes, 23 pairs. And most of your cells look like the cells on the left, where there's a pair of chromosome 1, 2, 3, and so forth. These chromosomes are painted with a specific chromosome specific paint so we can distinguish which one is which, and this is a so-called normal karyotype.

Cancer cells can look like this. And you can see that they're different in many respects from normal cells. A, there's way too many chromosomes. This is a condition we call aneuploidy. Aneuploidy, as opposed to being diploid, the cells are aneuploid, an abnormal number of

chromosomes. Moreover, you can see in some of the highlighted areas that the chromosome structure is abnormal. We have this chromosome here, which has a little bit of the pale blue chromosome-- which may be chromosome 4, I can't read it-- and a little bit of this pink chromosome, which is one of these guys here.

A translocation has taken place so that the structure of the chromosome is abnormal. So we have aneuploidy, defects in chromosome number, but also defects in chromosome structure, like translocations. We also have deletions-- not easy to see in this slide-- where chromosomes have incurred big losses of genetic material. OK? Chromosome abnormalities in cancer have been known about for a very long time.

A second and very important observation, which occurred sometime in the '40s-- maybe '30s, '40s, and '50s-- and built up over time since then, is that carcinogens, carcinogens, which are cancer causing agents, are almost always mutagens, which are mutation causing agents. So something that can cause cancer in, for example, a laboratory animal, can be shown to alter the DNA and cause mutations. That would suggest that the carcinogen is acting through the alterations in the DNA.

And this observation was made much more convincing through the work of an investigator by the name of Bruce Ames, who developed the so-called Ames test. And I want to tell you about that. But actually, before I do, let me just show you graphically how the agent can be tested for its carcinogenic capabilities and its mutagenic capabilities. The carcinogen is tested by treating an animal-- a mouse or a rat-- injecting the animal with the carcinogen or painting the carcinogen or the potential carcinogen on the skin of the animal, and then waiting a certain amount of time and asking the question whether the animal developed a tumor.

And you can do this with different doses of the agent, with large numbers of animals, and actually get quantitative data that tells you the potency of this potential carcinogen. So that's the carcinogenesis assay. To test whether something is a mutagen, you can take the agent and treat cells and ask whether you can cause mutations in those cells. You could do this in lots of different types of cells. But the easiest types of cells to do it in are bacterial cells, for example, salmonella bacteria or E. coli.

And the way this assay is done is to use cells that are defective in the production of an amino acid, let's say histidine. So the cells have mutations in a biosynthetic enzyme-- and I'll tell you more about this in a second-- that is required for the cells to make histidine. Now these cells

can live if you provide histidine to them exogenously, for example, on the Petri dish. But if you take those cells and you plate them on a Petri dish that is lacking histidine, none of the cells will be able to grow because they require exogenous histidine to live.

However, if you take that mutagen and you add it to these histidine minus cells, the mutagen might correct the mutation in the histidine biosynthesis gene, thereby converting it to a wild type form at some low frequency. Such that if you plate these now mutagen-treated cells on a histidine minus plate, you might get a few colonies growing. And these would be histidine plus, capable of producing histidine themselves, revertants. They've reverted the mutation to now a wild type form. OK?

And it was this that was the basis of the Ames test, to test the mutagenicity of potential compounds. Now we actually use different versions of his minus bacteria, because different mutagens cause different types of mutations. And if you use just one mutant bacteria, you might miss certain potential mutagens.

So for example, if we have a specific mutant, which is in a gene required for the conversion of histidinol, in an enzyme that is called histidinol dihydrogenase, this enzyme is required to produce histidine in the final step of the synthesis. The wild type enzyme would have a particular sequence, which would encode a particular pair of amino acids, glutamine and serine. And it is this collection of histidine minus bacteria, this collection of histidine minus bacteria that we use in this assay, we might have one mutant, which has an alteration, which converts that C to a T.

This creates a termination codon. So this is why that bacterium can't make histidine, because it can't make that enzyme. It has a stop codon on that position. A second mutant might have a different stop codon. This is determination codon. Here, this C has been converted to a G, creating the stop codon. And a third mutant might have an abnormal number of bases in this region, an insertion of an A residue, which would cause a frame shift.

These are three different mutants, which would require three different types of alterations in the DNA to convert back to the wild type. Here, this pyrimidine would have to be converted to a different pyrimidine. Here, this purine would have to be converted to a pyrimidine. And here this abnormal number of bases would have to be corrected to the correct number.

This would allow one to find agents which function as point mutagens, which is a class of mutagens. They create point mutations. And this type of bacteria would allow you to find what

are called frame shift mutagens. So these bacteria are mixed together. The mutagen is added. And then you count the number of cells that survive on the his minus plate. That's the original Ames test.

As Ames and others continue to do this kind of testing, they discovered, to their surprise, that some clearly established carcinogens failed the Ames test. They cause lots of tumors in animals, but they didn't revert any bacteria in that bacterial assay. So can anybody think why that is? Why might an agent, which can clearly cause cancer, fail that test?

Well, one answer-- and the most common answer-- is that the agent itself is not itself a mutation. But it can be converted in the body through the process of metabolism. As your body tries to convert that agent into something, for example, that it can excrete, it alters it chemically and converts it from a promutagenic form into a mutagenic form. And in this form, it can cause mutations in your DNA, and in theory, in the bacterial cases as well.

And here's an example of a promutagen called benzo(a)pyrene, a very important mutation in cigarette smoke. This is converted, through various steps inside your liver, to a form that is much more mutagenic. These epoxides are much more mutagenic compared to the original compound, much more reactive, much more reactive to DNA. And in these forms, the compound will actually covalently attach to the bases of DNA and cause mutations. OK? So in this sense, your body is actually part of the problem. It's trying to get rid of this bad stuff, but in the process of doing that, it's making it worse.

Recognizing that this was an issue for actually quite a few potential mutagens, Ames and others modified the Ames test. It's now called the Modified Ames test. In which case, you take the compound of interest, the potential mutagen, you mix it with some extract from liver to allow this metabolism to occur. And then you take those, the metabolized compound, and you do the bacterial, the bacterial mutagenesis test that I just reviewed for you. OK? And now you find that many of these things that failed initially, score positively.

OK. So stuff that we get exposed to, like benzo(a)pyrene, and other agents in the environment, can cause mutations, and these can also cause cancer. I just want to take a few seconds to rail against tobacco smoke and cigarette smoking. Lung cancer is the most common form of cancer in this country. 175,000 deaths due to lung cancer each year. About 150,000 of those deaths are due to smoking. It's the most common form of cancer, and among the most preventable forms of cancer, through to the failure to expose the body to

carcinogens in cigarette smoke.

Not only is there benzo(a)pyrene in cigarette smoke, but there's about 1,000 other carcinogens in cigarette smoke. Cigarette smoking is still very common in this country, remarkably common in this country. About 46 million adults still smoke in this country. A remarkable number of high school students still smoke in this country. And it's because of this that lung cancer rates are still very, very high. Moreover, smoking causes all sorts of other diseases-- emphysema, kidney diseases, cardiovascular diseases.

It's now estimated that among the however many billions of people are on the planet today-- what's that number, 6 billion people on the planet today? Something like 650 million of them will die due to the exposure to cigarette smoke. So my little lesson here is that if you're currently smoking, stop. If you're not smoking, don't start. It's the easiest way to protect yourself against many, many dangerous future problems. All right. So cigarette smoke is something we do to ourselves. We expose ourselves to mutagens that cause cancer cells to develop in your lungs and in other parts of your body.

There are other so-called exogenous mutagens, things that we get exposed to. Sunlight, for example, sunlight, the UV rays in sunlight, can cause damage to your DNA, causing skin cancer and melanoma. Dietary carcinogens, barbecued beef, has certain dietary carcinogens in the category, actually, of benzo(a)pyrene, that can cause damage to your DNA and induce colon cancer. Not at high numbers, not saying you shouldn't eat barbecue. But still, this is an example of stuff we get exposed to that increases our cancer risk.

Replication errors. Your cells are good at copying the DNA. They're very good at it. They have proofreading functions that make them better at it. But they're not perfect. So every time your cells divide, you actually run the risk of making a mistake. And replication errors are a common source of mutations in cancer. As your cells are moving DNA around, they also sometimes break it. And these DNA breaks are sometimes sealed properly, but sometimes not. And deletions can occur. And translocations can occur. And another endogenous process that leads to mutations, including in cancer cells.

Defects in DNA repair. You have lots of enzymes that are looking at your DNA at all times for adducts that have formed, and other alterations. And those enzymes remove those damaged bases and fix them. But sometimes they fail. Sometimes they actually get mutated in cancer cells, raising the risk still further. So defects in DNA damage and DNA damage repair

enzymes.

Your cells also produce endogenous mutagens. Various reactive oxygen species are produced, for example, in the process of metabolism. And these reactive oxygen species, like superoxide, hydrogen peroxide, can interact with the DNA and cause mutations. This is why antioxidants are useful in preventing cancer in some settings. OK? So various things that we get exposed to or we expose ourselves to cause mutations in DNA. And this results, ultimately, in the development of cancers.

The last thing I'll mention to you is that this doesn't happen overnight. It's not that a single alteration in a single gene is sufficient to derive tumor development. Instead, it's a process that occurs over time and requires alterations to many genes. So if you imagine a cell, a normal cell, which divides to produce two daughters with the same DNA content, at some frequency, this cell might acquire a mutation. Maybe it got exposed to cigarette smoke. Maybe it got exposed to superoxide. Maybe it made a mistake.

And this mutation then confers upon that cell the ability to divide especially well. And now all of its daughter cells carry that same mutation. And as that cell divides further and produces daughter cells of its own, perhaps one of those cells-- and this might not be in the very next cell division, it might be five years later-- one of those cells acquires a second mutation. And that mutation gives that cell the ability to divide even more rapidly, or survive even better. And again, all of its descendant cells will have that same abnormal genotype.

And maybe within that clone of cells, a third mutation takes place. And on and on we go. We now think that we need somewhere between 5 and 10 mutations in cellular genes to allow the cells to progress all the way to that full blown cancer that I showed you in pictures before. So this process continues until we have true malignancy. And this process of developing clones with increasing ability to develop into cancer, we call the clonal evolution theory, the clonal evolution of increasingly abnormal clones, which eventually will develop into a cancer.

And next time we'll talk about what are the genes that are mutated in these developing cancers.