Yale Cancer Center Answers

Therapeutic Radiology and Human Genetics

Guest Expert:
Joann Sweasy, PhD
Professor of Therapeutic Radiology and of Genetics, Yale School of Medicine

Yale Cancer Center Answers is a weekly broadcast on WNPR Connecticut Public Radio
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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you could submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week is a conversation about DNA and the role that it plays in cancer with Dr. Joann Sweasy. Dr. Sweasy is Professor of Therapeutic Radiology and of Genetics at Yale School of Medicine. Here is Dr. Steven Gore.

Gore DNA and the role it plays in cancer, that is a big topic!

Sweasy Huge topic.

Gore Why don’t we get started with that. What is your interest in DNA, tell me about genetics and cancer.

Sweasy What I am really interested in is DNA repair and cancer, so if DNA is improperly repaired, cancer can develop.

Gore Why do I need to repair it in the first place, my DNA is not broken, is it?

Sweasy DNA is damaged, 20,000 base damages per cell per day just from breathing and metabolizing oxygen.

Gore So the bases are the letters, right?

Sweasy Bases are the letters.

Gore A, T, G and C.

Sweasy You got it.

Gore Wow, so 20,000 a day?

Sweasy 20,000 a day.

Gore Just for metabolizing oxygen?

Sweasy Oxidative damage, reactive oxygen and nitrogen species, damage to bases.

Gore I want a new system, I am trading mine in. That is kind of scary.

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Sweasy That is right, that has to be repaired and many times it is not repaired properly, and so when it is not repaired properly, mutations result and those mutations can lead to cancer.

Gore I have got a very good repair system, I am sure of that.

Sweasy Actually, now that we have the genomic sequencing in 1000 genomes, we are learning that that is really not the case and that a lot of people have variants in DNA repair genes or mutations in DNA repair genes just in their germline. We are not sure that all of them mean anything. They have not been studied, but there are thousands and thousands of these variants now.

Gore Wow, you are bursting my bubble. So here I am breathing oxygen like a fool.

Sweasy Do not breathe it.

Gore Then I am also in trouble, so it is a risk-benefit ratio as I need my oxygen, so I am breathing oxygen, and I am getting 20,000 mutations?

Sweasy 20,000 DNA damages per cell per day.

Gore Damages, of which some are going to be repaired properly.

Sweasy The majority hopefully will be repaired properly.

Gore I am hoping so. But some of them not so properly, perhaps and sometimes that is going to lead to mutations.

Sweasy Sometimes that will lead to mutations and then sometimes these mutations will lead to cancer. We are not even in this case taking into account the effects of using light, so that is just oxygen, so we now put UV light on top of it and we know that UV light leads to skin cancer.

Gore So now I am going to start breathing nitrogen and staying in the dark, is that what you are telling me?

Sweasy That might not be good either.

Gore Have you been watching this new show Better Call Saul?

Sweasy I have not, but I would like to see it.

Gore It is a prequel to Breaking Bad, and one of the characters in it has decided he has got an allergy to electromagnetic radiation, so he is totally off the grid. He has disconnected all the electricity in his house and will not let anything enter. Anyway, that was really off topic.

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Sweasy: But that is okay, I like that.

Gore: So don’t cells sometimes recognize that they have mis-repaired and decide they are good for nothing cells and kill themselves off, is that what happens sometimes?

Sweasy: That is exactly right. Cells can recognize that and they can kill themselves off. That is a very good process. The other point though that I would like to talk about with DNA repair is that we have to think about DNA repair in terms of cancer therapy because most of the cancer therapies that are used now damage DNA and that is the way they work, only they work by irreversible damage in DNA. So if they damage DNA, as you just mentioned, the cells die if there is a irreversible DNA damage. The flipside of that is that if the repair system is working really well in the tumor, then the tumor becomes resistant to those cancer therapies like ionizing radiation or more like chemotherapies.

Gore: What about things in the environment, you mentioned, ultraviolet radiation, that’s key, and what about like toxins in the environment, benzenes around, smoking, is this all the part of the same thing?

Sweasy: It all damages DNA, right.

Gore: It sounds like that is really the basis of many if not all cancers.

Sweasy: DNA damage.

Gore: But I guess there are other reasons.

Sweasy: Right, but we do know that there are lots of mutations in cancers and in a lot of tumors there are many mutations and so there is the mutational theory of cancer which suggests that the accumulation of mutations or the mutation rate of a cell actually leads to cancer. If you have a high mutation rate, you can have cancer.

Gore: So in most of us who are of a certain age, if we were to look at our cells and sequence them, would most of us find mutations even if we were healthy?

Sweasy: Oh absolutely, just in our blood cells or cheek cells absolutely. We find lots and lots of variants. I just actually had my whole genome sequenced.

Gore: You did, wow.

Gore: Do not tell your insurance company.

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Sweasy: The average number I think of single nucleotide polymorphisms in a person is about 200,000.

Gore: That is single letter misspellings, right?

Sweasy: Single letter misspellings, about 200,000, and we do not know what they all mean. We do not know what the majority of them mean.

Gore: Are most of them in genes or are some of them in the parts of the DNA that are like the dark matter that are not genes?

Sweasy: They are in between the exons, they are in between, most of them are in the coding matter.

Gore: Most of them are in the noncoding.

Sweasy: I am sorry, the noncoding matter. Most of them are in introns in the noncoding matter.

Gore: The part that does not spell for protons.

Sweasy: Right, but we know that those introns now are becoming very important in gene regulation and directing what the gene actually does or when it is expressed.

Gore: You are making me very upset. But I guess many people have survived for millions of years with all these polymorphisms, right.

Sweasy: That is exactly right.

Gore: Although they were not exposed to all the horrible stuff that we put into our environment. Interesting, are you actually studying the impacts of radiation considering therapeutic radiology, is that part of your research?

Sweasy: Part of my research is actually looking to find out which or what combination of DNA repair mutations or mutations and DNA repair genes work with ionizing radiation or radiation to kill cancer cells.

Gore: So you are trying to kill cancer cells better.

Sweasy: Right.

Gore: You are not really looking at what is causing the cancer.

Sweasy: We are doing both, but in this case with radiation, we are looking to see how to treat cancer better.

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Gore  So combining radiation with DNA repair mutations? How do you get mutation on purpose?

Sweasy  It can be in the tumor.

Gore  Oh gotcha, if my tumor already has one.

Sweasy  If your tumor has one, for example, tumors that might have BRCA mutations.

Gore  That is the one involved with breast cancer.

Sweasy  Exactly, some of those tumors might be more sensitive to radiation, at least initially.

Gore  We use a lot of radiation for breast cancer.

Sweasy  Right, exactly.

Gore  So is your thought to target radiation to certain individuals whose cancers are more likely to be responsive and not use radiation if we think they are not going to be satisfactory?

Sweasy  We are actually looking into that and we are trying to find a DNA repair gene signature that might be a good signature to indicate that we can treat that cancer with radiation.

Gore  But there are also drugs that are inhibiting DNA repair, right?

Sweasy  Right, so there is a new drug called a PARP inhibitor that was just recently approved by the FDA.

Gore  PARP, I did not realize that any of them have been approved, wow. What is it approved for, do you know?

Sweasy  I am not really sure, I think probably breast.

Gore  To be used with chemotherapy?

Sweasy  I do not know if it is single agent or not.

Gore  So we have studies, these so called PARP inhibitors in many tumors, and I did not realize any of them have gotten as far as FDA approval. It is very interesting. So the idea there is to poison the DNA repair machinery?

Sweasy  That is correct. It poisons one form of DNA repair, leading it down to another form of DNA repair which in the tumor would then be crippled because of the mutation. That is exactly the way it works.

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Gore: How many forms of DNA repair are there?

Sweasy: Lots, at least six, some people would argue more.

Gore: Six.

Sweasy: There are at least 170 genes that are bonafide DNA repair genes.

Gore: Wow, interesting, so do you focus on sort of one or the other?

Sweasy: I am interested in two major pathways of repair, base excision repair which is this repair of pathways that handles all of the damage created by oxygen. And I am also interested in recombinational repair.

Gore: What does that mean?

Sweasy: That is repair, the BRCA mutations, the BRCA genes, they work in that where two strands of DNA recombine with each other to repair a double strand break, for example. A DNA is broken, so it repairs broken DNA.

Gore: Double stranded breaks.

Sweasy: Right.

Gore: And I remember there is something non-homologous end-joining, which was one kind of repair.

Sweasy: So that repair breaks and that puts them together usually incorrectly, many times incorrectly whereas the combinational repair is more error free, so it is the preferred way of repairing the DNA.

Gore: What does the body have ways that seem like they would make mistakes? Why would the body want to, again obviously you are not the creator, you do not have insight, but do you understand why we have these pathways that seem like that may cause more trouble than they are worth.

Sweasy: I think the reason we have all these pathways is that the enzymes or the proteins in the pathways recognize specific types of DNA damage. It is all in the specificity of recognizing the damage.

Gore: So we evolved to see different kinds of problems and do the best we can to fix them.

Sweasy: That is exactly right.

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And sometimes we evolved better than others. I guess the good news from an evolutionary standpoint is that because most cancers are present in kind of post-reproductive people that we do not select against these mutations, the development of these enzymes that make mistakes, if they do not cause cancers after you have kids.

Right.

DNA does not really care if it makes a mistake.

Cancer is a disease of aging. You have to accumulate the mutations, proliferate, divide and make a tumor, it takes a long time.

Do you have any idea how long that actually takes, I think it is something our audience may be interested in? Do you have any idea about that?

What we do know is if you deliberately damage DNA because you are treating a patient, for example a child, or the other example we have is the atomic bomb survivors’ database. So we know that it takes about 30 years for a cancer to develop after the initial insult with the initial treatment.

Clearly after the atomic bomb episodes, catastrophes, there were leukemias that developed earlier than that.

They developed earlier, but mostly in children actually they developed a little bit earlier.

Take your time. See we scientists have a lot of fun for the listening audience, it is not all real serious stuff.

My understanding is that a lot of them took 20-30 years.

I recently heard somebody speak, a Japanese investigator, who is still very involved in the follow-up and there are still increased incidents, I am pretty sure of cancer compared to age-matched controls or whatever, even so many years after the episodes of Nagasaki and Hiroshima.

Right and now that what we are beginning to collect data, we have a lot of data on children who were treated for childhood cancers and the rate of secondary malignancies is between 20 and 30%.

No kidding.

And that takes about 20-30 years to manifest itself.

So I cannot breathe oxygen, I cannot go out in the light and I cannot be cured of my cancer?
Sweasy: Well it is 30 additional years.

Gore: That is an extremely good point.

Sweasy: It really is a good point.

Gore: We are going to follow-up on this after our break, but right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about our DNA and DNA repair and cancer with Dr. Joann Sweasy.

Medical Minute: The American Cancer Society estimates that there will be 75,000 new cases of melanoma in the US this year with over 1000 of these patients living in Connecticut. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key and when detected early melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for melanoma. The goal of the specialized programs of research excellence SPORE in skin cancer grant is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improve the diagnosis and treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut’s Public Media Source for news and ideas.

Gore: Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by my guest Dr. Joann Sweasy and we are discussing our DNA, the way we fix it, genetics and cancer. I feel like this show is “Me and my DNA.” So why did you decide to have your genome sequenced?

Sweasy: Well I was asked to do it as part of a control. I am a control.

Gore: So we are assuming you are normal. She looks normal for the studio audience.

Sweasy: I thought it would be great, I had a whole genome sequence to every single base.

Gore: Wow.

Sweasy: And the report was evidence based things and it turns out that I do not have anything, so it is great. I feel really good about that. But I cannot sue them if I find out that I do have anything later on.

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Gore Was that done here, was it a part of a Yale Program here?

Sweasy No it was done at Mount Sinai and now I have the disc drive with my sequence on it.

Gore What are you going to do with it?

Sweasy I am going to put it on my coffee table.

Gore Is it a whole hard drive?

Sweasy Yes.

Gore No kidding. How much data is that?

Sweasy A terabyte.

Gore Wow.

Sweasy That is huge. That is a lot of data.

Gore And by the time you are ever going to need it probably, the hard drive, there will be some other technology and it will not be readable anymore.

Sweasy I know, so I have been looking into that so that I can be transferring it to whatever technology.

Gore There you go. I actually did 23 in May last year, which was a commercial thing to look for polymorphisms and some of the audience may have done it as well and I learned that I am 95% Ashkenazi Jewish which was no surprise to me but it was kind of interesting to have it confirmed. Interestingly, the 5% that was not it, although there is some Neanderthal DNA in there which does not surprise my wife, but the 5% that was not was Mongolian and it was always said that my mother’s father who was from the Russian Poland border looked very Asian and there is always the thought that there had been some Huns around.

Sweasy How interesting.

Gore Yeah Genghis. So you were telling us before that many of us have polymorphisms or variations in our many 100s of DNA repair enzymes, can we take advantage of that in terms of therapy for cancer?

Sweasy I think we can, here at Yale we have a Precision Medicine Tumor Board and what that does is part of it is sequencing tumors and so all the doctors sit around and talk about the DNA sequence and sometimes DNA repair.
Gore It sounds really thrilling, well I thought was going to be a G but it was really a C, how long can you keep that up for.

Sweasy That is okay because sometimes we find what we call actionable mutations and for example, if someone has a BRCA mutation, we know that we can treat that cancer with a PARP inhibitor.

Gore Now that one is approved.

Sweasy Right, so we can treat that and that is really very exciting but there are so many polymorphisms, we call them SNPs, these mutations in genes and then in repair genes that come up, that we do not really know that much about, no one has ever really studied them and so what my lab likes to do is to study these SNPs in cells and in mice to figure out what they do and how they repair DNA correctly because if they cannot repair DNA, for example, then we can exploit that, combine them with a drug to kill the tumor. And we can combine them with the drugs people already know about. We do not have to go out and find new drugs. These are drugs that are already on the market and we can test to see if they work with this bad DNA repair gene.

Gore Is that the same thing as synthetic lethality?

Sweasy It is exactly synthetic lethality.

Gore Which is a word I have never liked but am starting to finally understand it. It is taking advantage of the Achilles heel to force the cell to die.

Sweasy That is right.

Gore How do you decide which of these polymorphisms are worth studying, I mean you tell me there are 100s of them.

Sweasy It is a difficult business, but we rely on crystallographers so many times the protein or similar proteins have 3 dimensional structure and they can look in the structure and make some predictions. Sometimes it relies on whether the algorithms or these mathematical programs that can be run by people called computational genomics experts and they can make some predictions and that is where that area is going in computational genomics. They can make some predictions and so we can at least narrow the list to the 10 or 20 interesting genes or variants that we can actually study, put into cells, put into mice.

Gore So in your grants are you studying like 10 or 20 really that you propose to do?

Sweasy We usually propose between 20 and 50 because now we have some high throughput screening that we can use to look at this.

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Gore: It sounds like a lot to me.

Sweasy: It is great and actually here at Yale we have screening facilities to do this with us. We have the Yale’s West Campus Facility, it is a drug screening facility, it is called the Yale Center for Molecular Discovery and we partner with them as with many of my colleagues to look at synthetic lethality.

Gore: So how do you do that? You start screening different drugs?

Sweasy: We screen different drugs, so what my lab does is we have a variant, a DNA repair variant expressed in the cell and we screen that against the 114 drugs that are already approved by the National Cancer Institute to treat cancer and we have many surprises where we have a variant that is highly sensitive to a drug that we never would have predicted otherwise and then many of my colleagues at the Yale Center for Molecular Discovery have all kinds of molecular libraries, so you can screen to find new molecules to treat these things.

Gore: When you say a library, we actually mean the little bits of the chemicals in tests.

Sweasy: Little bit of chemicals.

Gore: And these are chemicals that are not necessarily drugs? They may be drugs, they may not be drugs right? They could just be chemicals off the shelf.

Sweasy: They may not be drugs, right, so one of my colleagues in my department, Dr. Ranjit Bindra has a drug that was used for another purpose and it looks like now it can actually treat cancer in certain circumstances.

Gore: How do you move from that? Let’s say you have got this polymorphism and you put in the cell and you find something that really kills those cells super well, but it was a psoriasis drug back in the 1940s or something, I am just making this up obviously.

Sweasy: Right.

Gore: What do you do next?

Sweasy: We have got to go into mice, so then you have to use xenograft models and you have to put tumors that have this variant in the mice and you have to treat the mice with the drug to see if it kills the tumor and if it does not kill the mouse, that is called therapeutic gain.

Gore: So we got a good therapeutic gain and these mice are happy and cured from the horrible tumors that you tried to poison them with. I am not trying to get the PETA people after you.

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Sweasy  Good.

Gore  Because animal research is super important, and I am a big believer and I am not disrespecting the PETA people either because I understand them.

Sweasy  We have to treat our animals well. If you do not treat your animals well and humanely it is a no go.

Gore  And we do not want to do research that is not valuable.

Sweasy  Absolutely.

Gore  So we find out that we can save our cute little Mickey mice.

Sweasy  That is the whole goal.

Gore  Right, we are curing them. But then what do you have to do? It seems like to go to the next step you have to get somebody interested like a company to say look at this data, help me make this into a real drug.

Sweasy  You have to try and do that and you can work with the Yale patent office to work that out to try and get venture capitalists interested. There are a number of investigators here at Yale who have done that successfully.

Gore  That is a huge step.

Sweasy  It is a huge undertaking right.

Gore  And I guess the National Cancer Institute and some of the foundations have ways of helping too, right?

Sweasy  That is right.

Gore  I know the NCI, used to be called the RAID program for making a lots of drugs for clinical trials, I do not think it is called that anymore.

Sweasy  Right.

Gore  So have you actually done that or are you still in the mouse.

Sweasy  We are still way pre-clinical. We are still in cells, we are moving into mice now.
Gore Obviously you cannot speak for other people, but is the motivation to carry this forward, the love of science and the real desire to cure people, is there a financial incentive if I get the golden bullet, we are able to get a patent and become rich and famous, what do you think drives people?

Sweasy Well in my experience, I think at least for my colleagues and my experience what really drives people is the science and being able to treat the disease. The financial gain is very nice but it is very rare. And there are so many people working in this area that it has to be for the love of science and for really trying to treat a disease successfully.

Gore I agree with you. Another institution that I worked at, they had some kind of seminar about trying to use the technology transfer office more and so on but really the percentage of these things that end up making money is so small that it seems like a very sort of misguided business plan. You are finance a cancer centre based on selling a bunch of drugs.

Sweasy No, that is not the way it works.

Gore But it is really cool when something was developed here at Yale or at any of these institutions and it becomes a reality and I know there is a drug called carfilzomib that was invented here.

Sweasy That is right.

Gore That is now a very important drug for the treatment of multiple myeloma, for example.

Sweasy Absolutely, and that was created based on very fundamental science, very basic science.

Gore So one of these days one of your mice is going to pay off. It gives me hope that maybe I can start going back into the sun, I am not really this paranoid about cancer.

Sweasy That is good.

Gore Do you participate in this Precision Tumor Board?

Sweasy I go when I can, yes, and it is very interesting to get different perspectives on the different mutations. Now remember that many of the mutations that come up are not necessarily in DNA repair genes. So there are a whole set of experts there in different fields to discuss these.

Gore And the nice thing about it I guess is having people to discuss across the table. You may have expertise in the DNA repair side of things, but somebody else may be interested in mitotic regulators. Cell-cycle regulators and things like that.

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And one of the other things we are interested in is most people are interested in the mutations that are exclusively in the tumor. We are also interested in the mutations that come from the person and they are called the germline mutations.

Why is that?

The reason that we are really interested in this is because we found that there are again mutations in repair genes in the person in the germline that actually confer resistance to chemotherapies.

How is that?

Well there are a lot of different mechanisms. It basically winds up that these mutations actually allow the person to repair their DNA better. So when they are treated with the cancer drug they repair their DNA better and so what we are trying to do is develop a way to find this out before a patient is treated because if a patient is just inherently resistant to a drug the drug will never work and again we can screen these mutations and we can find what they are resistant to and what they are sensitive to. For example, we have a mutation right now where people would all be resistant to cisplatin and this is a cancer that is normally treated with cisplatin. These people never do well and we know the reason. We could put them on another drug when we have several of them and it would be successful but these drugs are not the usual drugs that are used to treat this kind of cancer.

But that is not currently in clinical practice yet?

It is currently not, it is moving in that direction because that is called personalized medicine.

I remember, if I am not mistaken, that in brain cancer currently people are screening for silencing of a, how does this work, there is a DNA repair enzyme.

MGMT.

That one, right. And it gets silenced through this process of methylation, am I right about that?

That is right.

And you can chose whether people are going to respond to a drug based on that test and that is being done clinically now?

That is being done clinically, right. So there is a precedent for this moving into the clinic.
Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.