



*Hosts*

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## The Role of Genetics on Cancer Risk

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*Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and the phone number is 1-888-234-4YCC. This week, Francine is joined by Dr. Joann Sweasy. Dr. Sweasy is Professor of Therapeutic Radiology and of Genetics at the Yale School of Medicine. Here is Francine Foss.*

Foss Can you talk a little bit about your background and what made you interested in the field of therapeutic radiology and then genetics?

Sweasy As a graduate student, I was very interested in DNA repair and I studied DNA repair and bacteria but became very interested in the mutator phenotype in cancer that was proposed by Dr. Larry Loeb, and so I went on to join his group as a post doc. The mutator phenotype says that there are so many mutations and tumors that they cannot be accounted for by the mutation rate of normal cells, and that has been shown to be the case in the Cancer Genome Atlas studies.

Foss Can you go through this process of DNA repair for us, what happens when DNA is damaged and how that process is ongoing in our cells?

Sweasy DNA is damaged, and DNA is damaged about 20,000 times per cell per day. So, it is a very high rate of damage. And what happens is that the damage is cut out by different proteins in the cell, and then the DNA backbone has to be patched up again by DNA polymerases.

Foss And what is it that actually damages the DNA that many times?

Sweasy Reactive oxygen species, the fact that we breathe and metabolize oxygen.

Foss And these antioxidants that we are supposed to be taking as part of our general health, do those help to prevent this process?

Sweasy It seems that they do in certain cases, but it probably is totally dependent upon your genetic background, and also your environment, what you are eating, etc.

Foss You mentioned that the DNA repair is important in cancer, can you tell us a little bit about how that works?

Sweasy I think the best idea so far is that if DNA repair does not work, it seems to be involved in cancer risk, and also if DNA repair works well in a tumor, it seems to be involved in resistance of the tumor to treatment. So, it is a double-edged sword.

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- Foss           What actually causes the DNA to be repaired? Are there certain proteins in the cell or enzymes that do this?
- Sweasy        There are many enzymes. There are enzymes that recognize the damage and cut it out. There are enzymes that break the backbone and there are enzymes that replace the backbone. One example of the way a cancer might work is an enzyme that has to patch in the backbone called the DNA polymerase. If that makes mistakes when it patches up the backbone, for example, instead of incorporating the base A opposite T, it incorporates the base G opposite T, that can be a mistake that results in a mutation that makes the cancer cell grow very quickly.
- Foss           So, these mutations are occurring all the time in our cells?
- Sweasy        Correct!
- Foss           What is it that prevents these mutations from causing cancer all the time then?
- Sweasy        Because it is sort of luck of the draw; in other words, it is random. So, if a mutation occurs in a key growth-control gene, a key regulatory region of the genome, that can result in cancer, but most of the time mutations do not occur in those areas.
- Foss           You used the term genomic instability to describe cancer cells. Can you talk about that? What is genomic instability?
- Sweasy        Genomic instability is thought of in a couple of different ways. One way is the accumulation of point mutations, just base changes in the DNA that result in cancer growth, but the second, and I think more commonly thought about, is chromosomal aberrations. For example, if DNA is not repaired correctly, double-strand breaks can arise so that DNA can be broken, and it can be misjoined. For example, parts of one chromosome, for example, chromosome 9 can be joined to chromosome 22, and that is known to be the case in leukemia, and it actually causes a new gene to be formed that results in rapid growth of the cells.
- Foss           So, the genomic instability is responsible for chromosomes basically breaking and rearranging differently?
- Sweasy        Rearranging differently especially, yes, that is the genomic instability.
- Foss           In some cases where there are these mutations, do they not lead to broken chromosomes?
- Sweasy        That is correct, in many cases, the DNA is repaired correctly. We have backup systems in our cells that repair the DNA correctly, but in some cases, it is not.

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Foss How does the patient actually know if they have any of these problems if they are having frequent breakage of their chromosomes?

Sweasy Usually patients do not just go in to find out if they are having frequent breakage of their chromosomes. One thing that they might do is if they are in a family with a high risk of cancer, they might want to have different tests done depending upon what type of cancer the familial risk is associated with, and then once they are diagnosed with cancer, certain technologies can be used, and they are used here at Yale, to diagnose the genomic instability, or sometimes, the mutation itself.

Foss How old are these patients that develop these familial syndromes?

Sweasy They usually tend to be younger, 40 years of age or less.

Foss And does this occur in children as well?

Sweasy It can occur in children, yes, but it is mostly young adults from what I understand.

Foss So, these patients are identified based on, as you said, the family history of certain cancers. And so they are identified as being potentially at risk for these mutations. Do they see a geneticist when they come in or how do they actually get into the system here at Yale?

Sweasy They do see a genetic counselor. Usually, they are from a high-risk family. In many cases, they have been diagnosed with a primary tumor, and they do go to see a genetic counselor.

Foss And are the tests that are done to look for the breaks in the chromosomes, are those tests done on the tumor sample or on normal cells, or both?

Sweasy They can be done on both, but if you are interested in finding out what the risk is, for example, for other family members or for your children, they are usually done on normal cells or germline cells to see if you were born with that mutation.

Foss So, I think the one that we are most familiar with in the news is the BRCA1 mutation associated with breast and ovarian cancer. Can you talk a little bit about that one?

Sweasy The BRCA1 mutation is very interesting. It was identified by Mary-Claire King some years ago, and it is a mutation, if you carry it in your germline, in other words, if you are born with the mutation, you are born with one copy of it, and then as you age, another mutation in the other chromosome occurs in the other copy, and that leads to a significantly increased risk for breast cancer over the normal population. What is interesting about BRCA is that it is a DNA repair

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gene. It is involved in coordinating double-strand break repair or the repair of breaks. And so, if you have a mutation in the gene, that malfunctions.

Foss So, basically, these women, as you said, they have one normal copy of the gene, but the second copy is lost?

Sweasy That is right.

Foss And that is picked up based on the genetic screening that you do?

Sweasy That is right.

Foss So at that level, you are picking up missing chromosomes and missing genes, but are you also picking up these point mutations that occur?

Sweasy You can. It depends on the method that you use to look. In most cases, the point mutations, they look for specific point mutation. For example, the BRCA test today looks for specific losses of chromosomes or point mutations, but there are probably other point mutations that are more rare, and these tests are not picking that up.

Foss So, they are not 100%?

Sweasy That is correct.

Foss There is another cancer that is associated with these kinds of syndromes, and that is the colon cancer story. Can you talk a little bit about those genes?

Sweasy One of the groups of genes that really interests me in colon cancer are the mismatch repair genes, and those are responsible for Lynch syndrome. Those are DNA repair mutations. And what mismatch repair does is it monitors DNA synthesis. As your cells grow, they have to make more DNA, and the mismatch repair system makes sure that it is made correctly. If it is not, it corrects the error. It is kind of like an eraser in a typewriter typing the correct things back in. And if that system is mutated or altered in any way, mismatch repair does not occur correctly and it results in colon cancer. There is another DNA repair gene in base excision repair that have mutated also results in colon cancer.

Foss Do these mismatch repair enzymes cause any other health problems other than cancer?

Sweasy They can. I believe they are associated with ovarian cancer and to a slight extent breast cancer, but I think they are most commonly studied in colon cancer.

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Foss And again, this is a test that could be picked up with genetic testing? This particular mutation can be easily picked up?

Sweasy Absolutely!

Foss And that would be done only in certain family cancer syndromes?

Sweasy Exactly, Lynch syndrome, especially.

Foss You do a lot of work on an enzyme called DNA polymerase beta?

Sweasy Yes.

Foss Can you tell us what that is?

Sweasy It is an enzyme that is sort of at the end of the repair pathway, and so after the damage is cut out of the DNA, this enzyme has to patch up the DNA. It synthesizes DNA. That is its major job.

Foss And how is this enzyme affected in cancer?

Sweasy It is sort of interesting. A while ago, maybe 9 or 10 years ago, we were thinking about this enzyme in terms of cancer, and we discovered that a lot of other lab groups had identified mutations in this gene in tumors, and then we have recently undertaken our own study here at Yale in colon carcinoma, and we are finding that this gene is mutated in a significant number of colon tumors.

Foss Is this a gene that is mutated only in the tumors themselves or is this another one of those genes that is connected with family cancer syndromes?

Sweasy This gene has not been connected with family cancer syndromes. It is only mutated in the tumor in this study although there are known germline variants of this gene, but to the best of my knowledge, no one has looked at them yet.

Foss And this is an enzyme that exists in all of our cells?

Sweasy Yes.

Foss And it only causes certain types of cancers if there are mutations?

Sweasy We do not know. In our study, we have only looked at colon tumors. The other studies have looked at a variety of tumors, but to the best of our knowledge, there is not functional evidence that a mutation of this gene results in the tumor.

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- Foss If there is a mutation of this gene, are there other ways that a cell can get around that?
- Sweasy At this point, we do not know. What we do know about mutation of this gene is that in some cases the mutants we find in tumors synthesize DNA incorrectly, and they cause mutations in cells that can result in the overgrowth of cells. In some cases, the DNA polymerase is inactive. And so, what happens is it does not patch up the DNA, and that results in breaks in the DNA that lead to what we talked about before, genomic instability.
- Foss As you are aware, we are talking about a number of different abnormalities that are occurring associated with the DNA and the enzymes around the DNA, in the average tumor, is there one mutation in one of these or are there multiple things going on at the same time?
- Sweasy We know there are definitely multiple things going on at the same time, the question is when there are lots of mutation in a tumor, which ones are the drivers, the ones that are actually causing the cancer, and which ones are just there, the hitchhikers, for example. And I think, now that we have a lot of sequences from tumors due to the Cancer Genome Atlas, we are beginning to understand and study the function of genes and variants that are found in tumors in order to figure out which ones are the drivers, the important ones, and which ones are just there for the ride.
- Foss And likewise, as we talked about variants in some of these genes like BRCA1, are there different normal variants of these polymerase genes say that may have different activity or make a person more susceptible to developing cancer?
- Sweasy Yes, we know that there are germline variants in all of our genes, and what is really interesting, I think, is to find out if these have altered function. Many of them do not, but some of them do.
- Foss This is really interesting talking about what is going on at the level of our DNA and understanding the genetics of cancer. We have to take a short break for a Medical Minute, but please stay tuned to learn more information about cancer genetics with Dr. Joann Sweasy.

*Medical  
Minute*

*There are over 11 million cancer survivors in the US, and the numbers keep going. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life-changing experience. Following treatment, the return to normal activities and relationships may be difficult and cancer survivors may face other long-term side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as the one at Yale Cancer Center, to keep cancer survivors well and focused on healthy living. This has been a Medical Minute, brought to you as a public service by Yale Cancer Center. More*

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Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined today by Dr. Joann Sweasy, and we are here discussing the topic of genetic risk and cancer. Before the break, Joann, we talked a lot about different mutations that occur in DNA repair enzymes and how those can all cause cancer. And what I am wondering is, are these found in all tumor cells or is there some heterogeneity between the tumor cells where some of them have these and some of them do not?

Sweasy In tumors, there is really a heterogeneity, and right now the Cancer Genome Atlas is probably picking up the dominant mutation, the one that is present and has been selected through the evolution of the tumor, but there are minor mutational changes in a small subset of cells, most likely, and what is important about those is that they are poised to make the tumor resistant, for example, to chemotherapy. If you treat the tumor with chemotherapy, it initially responds, and then after a while, it can become resistant, and it is likely due to those DNA repair mutations.

Foss How do we know if those small populations of cells exist in a number of patients that we are treating, and is there anything we can actually do about that if we know?

Sweasy At this point, we do not know a lot. What my lab is doing is we are characterizing the DNA repair landscape of tumors by capturing and sequencing all the DNA repair genes and tumors.

Foss And how many is that?

Sweasy Right now, it is about 220 genes.

Foss And how much work is that? It sounds like a huge endeavor, how do you actually do that?

Sweasy What we do is we use a capture chip that actually is able to take all the DNA and you mix it with this chip, and it can just pick out the DNA repair genes by the way we have designed the chip.

Foss So, you just take a piece of a tumor from a patient?

Sweasy Right.

Foss And you put it on this chip and then what?

Sweasy And it just picks out all the DNA repair genes, and then we put that into the genome analyzer, which is new technology for sequencing, and in just a few hours, all the sequences are spit out of the genome analyzer.

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Foss That sounds pretty impressive!

Sweasy It is very interesting. The issue then becomes, we have all the data, and so we collaborate with bioinformatics experts here at Yale to tell us what it all means.

Foss How do you interpret all that data, say from 200 tumors and you have got multiple genes that you are looking at, how do you figure that all out?

Sweasy First what they have to do is called mapping it to the reference sequence. There is a reference sequence in the database at the NIH, and they map it to that to weed out all of the things that are already there. And then, from that they can select only the DNA repair mutations in the tumor.

Foss When you do this, how many of these mutations do you actually come up with?

Sweasy We have just initiated our studies but our initial studies suggest that we are coming up with very interesting mutations, I would say, somewhere on the order of 40, in the first tumor that we have sequenced, the first couple of tumors that we have sequenced, only in DNA repair genes. And when I say 40, I only mean in the coding regions of the genes, the parts of the genes that actually make the protein. There are many other mutations, but we really cannot study them at this point.

Foss Can you explain for the audience, why it is important to look in the coding region?

Sweasy The coding region is the region of the genes. We have genes and we have exons that code for protein, and we have introns that are in between the exons. And when the protein is made, the introns are spliced out, the exons are put together, and so then we have a protein. That is what actually goes on to repair the DNA. So, we are looking for mutations in those exons that make the protein so that we can find out if the DNA is not being repaired anymore.

Foss Some of these mutations will cause the protein not to work, but are other mutations that would not affect the protein?

Sweasy Yes, there are many mutations that might not affect the protein. So, that is the next step and that is a very important step, and that is to find out how the protein has changed and it is possible that the protein might no longer repair DNA.

Foss In the process of doing this, you look at multiple tumor cells from any individual patient?

Sweasy Yes.

Foss And I think we already touched on this point but do most of those tumor cells have the same

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mutation, or are you going to be finding multiple mutations, say in the same patient and the same gene?

Sweasy Up until now, we have not found a lot of multiple mutations, but we have a very small sample size. We could, nobody really knows.

Foss What kind of tumors are you studying right now?

Sweasy Breast cancer.

Foss And what are you proposing to do next?

Sweasy Once we identify the mutations that are present, and we are focusing right now on triple-negative breast cancer, what we would like to do is make those proteins in the lab and study them to see if they can no longer repair DNA appropriately.

Foss Will you actually go back to the original tumors in the patients as well?

Sweasy It would be good to do that. At this point, we do not have funds to do that, but it would definitely be good to do that; the other thing that we would like to do is put these mutated genes into human cells and ask how the human cells respond to cancer therapy. In other words, do these mutations make the human cells resistant to cancer therapy and cancer drugs?

Foss At this point, has this research actually been translated into patients at the bedside? Are we taking this knowledge yet directly to the patient?

Sweasy We have not done that yet. What we are doing is taking patient samples and finding out what is in them in terms of mutations. The other thing that my lab has done is to set up a model of a humanized mouse model of breast cancer. And so what we are doing is, we are reconstituting the human immune system in a mouse with a breast tumor and seeing how that responds to therapy.

Foss Can you talk a little bit about the humanized mouse model system just so that our audience understands what that is?

Sweasy A mouse has an immune system and a human person has an immune system, and that is the system that fights off infections. And we also think that the immune system has a lot to do with the treatment of cancer. So, the human mouse model of cancer is a mouse that has some human immune system genes in it, and then the other thing that we do is we inoculate it with blood cells from a human, and those blood cells expand and essentially reconstitute the human immune system

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in the mouse. So, the mouse now has a human immune system.

Foss Why is it important to study breast tumors in this kind of a mouse?

Sweasy Because a mouse immune system will respond to a human tumor in a totally different way than a human immune system will respond to a human tumor.

Foss Joann, this is really cutting-edge work that you are doing.

Sweasy I think so. It is very exciting!

Foss And what are you hoping to learn from these animal models? How are you actually going to use them?

Sweasy The idea is that most of the drugs that are found in cell line models and that go through the normal type of mouse model, and into the clinic do not make it. About 20% of the drugs are actually shown to have some sort of good therapeutic index. And we think that part of that is due to the fact that the wrong models are being used, and that we really need to use a humanized mouse model so that we have a human immune system with a human tumor.

Foss This mouse model system would be used say to test new drugs or new therapies that we think might be effective?

Sweasy That is absolutely true.

Foss And that is mainly because the existing systems, as you point out, are not that predictive, so what might work in a mouse does not work in a person.

Sweasy That is absolutely true.

Foss Can you tell us a little bit more about where your research is leading at this point?

Sweasy Where it is leading is we are very interested in the DNA repair landscape of tumors, and the mutations that we are going to find in tumors. We are very interested in characterizing which mutations in tumors could actually drive cancer and which ones are just there because they are hitchhikers. We are very interested in expanding our human mouse model of cancer and looking at some of the mutations that we find to find out if they actually cause drug resistance of tumors.

Foss Joann, you are involved with the Biological and Biomedical Sciences Program at Yale, which is a new program. Can you tell us about that?

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- Sweasy Sure, it is a graduate program. It is an umbrella graduate program and there are eight different tracks. Tracks are like the topics like Genetics, or Pharmacology, or Immunobiology. And students apply to those tracks and are accepted, but once accepted, students do rotations in labs to see where they would actually like to do their PhD. And they can join the lab of 1 of 290 participating faculty members. So they have a huge choice here. They keep coming to the pharmacology department and eventually wind up in the genetics department, for example.
- Foss And why is this important for us as a training institution and why is it important for the people that are coming in as PhD students?
- Sweasy Biomedical research, in my opinion, is no longer just a single field. Biomedical research is actually many different fields collaborating with each other. And so we need to give our students a choice as to where they would like to train and which people they would like to work with and collaborate with.
- Foss And is this program being conducted both here and at the facilities, the new Yale facilities on West Campus?
- Sweasy Yes, the graduate students who eventually join principal investigators there will also be part of this umbrella program. The other thing that the umbrella program does is it funds the graduate students, and it also has different symposia and seminar speakers etc. for students to get together, listen to, and talk with.
- Foss Can you talk a little bit about the whole field of genetics, of cancer genetics? We have touched on this now a number of times, and certainly that field is evolving. Where are we today with cancer genetics?
- Sweasy Today we are in a couple of different places with cancer genetics. I think one of the most astounding technologies available to us today is the ability to sequence an entire genome, and that is being done here at Yale. I understand that we actually are sequencing the most number of bases of DNA in the United States right now per day.
- Foss We are?
- Sweasy That is what I heard from the man who runs the facility, Dr. Shrikant Mane.
- Foss And how long does it take to sequence say one person's DNA?
- Sweasy One person's DNA, I think it takes about a week, but I am not really sure about that.

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Foss Continuous 24x7?

Sweasy 24x7. Putting the DNA out is also getting cheaper. What we have learned from the Cancer Genome Atlas Program is about all the mutations in a number of different tumors, and also, we are learning about germline mutations, people who actually have mutations in their germline DNA. Now, it is time to start to understand the functions of these mutations, whether mutations in the germline contribute to cancer risk, and whether mutations in the tumor are going to impact therapy.

Foss And how do we go about doing that?

Sweasy In my mind, we have to study the individual variants one-on-one although we have new fields now, for example, systems biology, which is predictive and also a lab science where people are getting together to try and figure out how a number of different mutations and altered pathways act together.

Foss So, basically just doing the sequencing and finding the mutations is only the beginning of the story?

Sweasy Absolutely!

Foss If patients out there are interested in this whole area of personalized medicine, should they be going after somebody to sequence their genome and how important is that to the individual patient at this point in time?

Sweasy I think not right now, and that is for a couple of different reasons; one, we have not sequenced enough genomes of enough different populations to really know what the reference sequence is. So we can call the mutations, but not as accurately as we would like to in order to predict risk or in order to predict benefit. And secondly, we do not really know what the mutations are doing. We know they are there. We know the tumors have lots of them. So we believe that they are causing the cancer, but we do not know how. And so at this point, since we do not know which mutations are important, I think it is not a good idea to have your genome sequenced at this point, unless, of course, you are a member of a high-risk family and the particular mutation is known, for example, we talked about the BRCA gene.

Foss So, in that case, they would only look at that particular gene?

Sweasy That is right, because we know how it works.

Foss In the context of personalized medicine in oncology where we talk about screening somebody's

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tumors, like the lung cancers and breast cancers for these mutations, is that something that you feel is really ready for primetime at this point?

Sweasy      It is almost there and there are some mutations that we do screen regularly at Yale because we know that they can be predictive of responses to drugs, and that is especially true, for example, in lung cancer.

*Dr. Joann Sweasy is Professor of Therapeutic Radiology and of Genetics at the Yale School of Medicine. If you have questions or would like to share your comments, visit [yalecancercenter.org](http://yalecancercenter.org), where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*