YALE CANCER ANSWERS

Cancer Research

Skin Damage and Repair

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April 23, 2017

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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Chagpar. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, Dr. Chagpar welcomes Dr. Douglas Brash for a conversation about skin damage and DNA repair. Dr. Brash is a Senior Research Scientist in Therapeutic Radiology and in Dermatology and Clinical Professor of Therapeutic Radiology at Yale School of Medicine, and Dr. Chagpar is Director of the Breast Center at Smilow Cancer Hospital.

Chagpar Doug, we hear a lot about sun damage and the fact that it can increase your risk of skin cancers and so on, and especially with summer coming up, a lot of people want to know how much importance they should put into it?

Brash I am glad you asked because it is something that we all tend not to think about. You like to go out in the sun, it feels good, you feel great afterwards, but it does have downsides and skin cancers actually are as frequent as all the other cancers combined in the US and people tend not to know that, even physicians because a lot of them are easily treatable and so we do not keep track of them, but some of them are not, some of them are lethal and all of them are easily preventable.

Chagpar Tell us more about the different kinds of skin cancers and how exactly the sun causes these cancers and what we can do about that?

Brash Your skin is an interesting organ. First of all, it is a very large organ. We tend to think of this a big piece of Saran wrap, but it is not and it has a lot of functions, like immune functions. It has two main kinds of cells – one is called keratinocytes, which are the ones that you think about that kind of hold your skin together, keep your insides in and water out; and the melanocytes which are less frequent and they are responsible for your skin color. So, each of those two cell types can cause cancer. The keratinocytes make two different kinds, one is called basal cell carcinoma which is very frequent but does not metastasize, it can be awkward to treat, so you do want to remove them and the other one is squamous cell carcinoma, which can invade and is a problem, so you want to get that removed as well. The melanocytes make melanoma, which are the ones that people worry about a lot and justifiably so. Those also, if you catch them early, are easy to treat, easy to remove and recently there are some therapies that are making progress even in the late stage, but what my dermatologist says is if you have a question, come and see me and I will be happy to tell you it's nothing, but go ask. So, all of these are linked to sunlight, you can get them without sunlight, but mostly it is

sun that is involved and we know because they appear on sun-exposed body sites, they are more frequent in Australia. But different tumors work in different ways. So, for example, squamous cell carcinoma is related to chronic sun exposure, like a farmer. The farmers tend not to get melanomas or basal cell carcinomas, and melanomas in particular are seen to be related to an acute sun exposure like the classic one is a bad sunburn in childhood. And so, years or decades later shows up somehow as a tumor.

Chagpar Okay. So, how exactly does the sun make these cells cancerous?

Brash For almost any disease, you do not get sick unless several things go wrong. And that is true here too. And many of the several things are triggered by ultraviolet light in sunlight doing different things. So, it becomes kind of a perfect storm. What ultraviolet light is, which is the photon, it is light you cannot see because actually nature is going out of its way to make sure it does not get into your eye because it causes problems. So, you cannot see it, but it is light, very high-energy light. The highest energy is called UVC. It never gets through the ozone layer and people tell me that it does not matter how much we deplete the ozone layer, UVC is not getting through, which is good because if it did, skin cancer would be a million fold more frequent than it is and we probably are dead long before the skin cancer anyway. UVB is lower energy. It does get through the ozone layer, just how much gets through depends acutely on how much ozone there is and that is why it's so important to maintain an ozone layer. And then, it causes DNA damage when it hits your skin. We can talk about that in a minute. UVA is the lowest energy, but is also more frequent in sunlight and it can get into your skin deeper, penetrate farther. It can also cause skin cancer, and until recently, it has not been all that clear how it works. I should say before how the UV works, not all melanoma is related to sunlight, some of it is tied to a nevi or moles that you get when you are young and some are related to sunlight causing different cancers and some not. So, people with dark skin like Asians or blacks have a lower frequency of skin cancers. They do still get skin cancers, but it tends to be related to the nevi, so not a sunlight related story or sometimes burn scars. So, these are all worth keeping an eye out for. Would you like me to tell you more about how UV causes all this?

Chagpar Yeah.

Brash It is a light photon, comes down out of the sky, you are on the beach, lands on your skin, the photons are absorbed by DNA, and it can also be absorbed by proteins and that energy is going to go somewhere, so it excites DNA, it rearranges the chemistry in the DNA and we can think of 4 letters ATG and C. The T's or the C's can get linked together and cause a bend in the DNA that causes problems. When you go to copy your DNA for a cell and it can cause cell death, it can cause mutations which were a

change in the information in the DNA and that is the sort of thing that starts you down the path towards a cancer. The UVA works a little differently. It is also absorbed by molecules, different set of molecules and we recently found out some brand-new chemistry we thought only happened in fireflies, but it also happens in us where we are still making the same kind of damage that took a second in the other story, but now, we can go on for hours after you leave the beach. So, you are driving home in the car, you are still damaging your skin in the way that can cause skin cancer.

Chagpar And so, you are lying on the beach and the UV rays hit your skin, they excite the DNA, the T's bind with C's instead of with A's causing bends in your DNA, so how come we still function after a day at the beach, like how come all of us do not get completely mutated?

Brash There is a paper that came out about a year ago where people sequenced this DNA in the skin and it turns out that by time you are 80, your skin is largely mutated and so it was actually a really interesting question, how do we function, because the skin is pretty normal. Now sunlight induces aging in skin, so there is a problem and it still functions nevertheless. Not all those mutations would lead to cancer, some of them may cause this little patch of skin to not work as well immunologically or in some barrier function or your skin dries out with age, those sorts of things. But the DNA damage is way more frequent than you might think. You go out to the beach and every cell has a million or so sites of DNA damage and your body mostly repairs those. It does actually a really good job, and in fact, the DNA base is the A's for the T's and the C's, nature has chosen them so they can absorb the energy and they turn it into heat really fast, so it is quite amazing, whereas very similar molecules do not do that. So, nature has evidently figured this out and there are diseases though where people cannot repair their DNA and they have a thousand-fold elevated incidence of skin cancer. So, your body is very busy trying to prevent all these things from happening, and mostly it keeps up. Visible light does not cause skin cancer if we think about it and that is actually rather clever on the part of nature, and it is only the ultraviolet light. The melanin is mostly preventing skin cancers by absorbing the light before it can go in, but again that energy goes somewhere and that is part of this other story we found about how we are making damage even hours after you leave the beach, so melanin turns out to be both good and bad. But there are variations around the world in melanin content, there are variations in other protective mechanisms and that is probably why some people are more sensitive than others.

Chagpar So, is the idea then that in order to prevent skin cancer, we have to stay out of the sun completely, which is impossible really, or is there a dose of sunlight that we should be getting, I mean people talk about vitamin D that we get from the sun? How

does that work or should we always be wearing sunscreen and do we need to make sure that that sunscreen says that it has got UVA and UVB protection and how all of this work anyways?

Brash For sure, if you are on the beach, you want the sunscreen that protects against UVA and UVB. We need the vitamin D. People tell me it is better to have the vitamin D that is made with sunlight and skin than getting it in your milk or in a pill. I cannot quite tell how significant that difference is. And so, how do you make this decision? When my wife and I had our daughter we were asking okay do we slather chemicals all over her every day, what do you do? I think the best advice is stay out of the sun between 10 and 2 or 3, wear a hat, long sleeves or something like that, and that will be the first line of defense. I think personally, go out in the sun and have a good time, just do not fry yourself. And related to that question is a question, isn't a tan good, is it not a good idea to get tanned to prevent skin cancers? It is true that if you have a tan from chronic sunlight exposure, you do prevent some kinds of cancer, you might cause other kinds, so it is not the greatest idea. A tan is really a part of the cell's SOS mechanism for, hey, I am in trouble, I got to do something, and so you will upregulate repair and you will also induce the tan, and the signal for the tan is the damage, so it does not necessarily mean you want to go out and damage your skin so that you can protect your skin. The best analogy I have heard is, if you did not want your office to burn down, would you set a fire in your waste basket to turn on the sprinklers so that if there ever was a fire, the sprinklers will be on? So, I think the optima is just to be reasonable.

Chagpar And so, when you say wear long sleeve shirts and a hat, are those protective against UVA and UVB, I mean can the energy still get through your clothing?

Brash Yeah, it can. Now, you can buy special clothing with SPF numbers, just like the sunscreens have. I am told that a T-shirt has an SPF of about 6, so it is not like wearing an aluminum foil, you are still at some risk, but probably you just do not go hiking on the beach at noon and that would be some benefit. I should say that that is not the official, I am not a dermatologist, I am a researcher. The official recommendation of dermatologist is stay out of sun, put on the sunscreen that kind of overlooks say the vitamin D story.

Chagpar So, talk to us a little bit about this story with melanoma and the idea that people who have melanin, right, because I think a lot of people who are naturally tanned, it is not that they are naturally tanned because of sun damage, but they got more melanin

and so they think of it as, or some may think of it as a natural sunscreen that protects them from UV rays, how much or how little of that is true, can they tolerate more sun than your usually fair-skinned red-haired, freckled neighbor?

Brash Epidemiologically, the frequency of skin cancers in Asians is about 10-fold less than in Caucasians and in blacks it is almost 100-fold less. And so, certainly, it is protecting. The people at highest risk of skin cancers are the blondes and red-heads. The thought for the longest time was blondes and redheads have lighter skin, so more ultraviolet light gets through the skin and that is why they have a higher risk. And one of the things that we found out a year or two ago is that the melanin, particularly from blonde and red melanin is chemically different than dark melanin. It has sulfur in it and the chemistry behaves differently and if you shine light on it or ultraviolet light off it, it shoots off electrons, it is really quite interesting at the chemical level. It turns out that if you radiate mice who have red melanin, you get more cell death, programmed cell death and we found out that what happens is when you irradiate skin that contains melanin, you start generating a couple, you help regulate some enzymes that make a couple different kinds of free radicals that combine and then they cause a chemical reaction in the melanin, that is just like what goes in fireflies except that instead of getting this nice, soft glowy, you get this very high energy level that is just like what you get when you are at the beach, and so that causes DNA damage and so the melanin is both helpful and harmful and the trade-off between those is dependent on whether you live in Australia or in Norway, it depends on whether you have dark hair or blonde hair and maybe it is just the best that nature could come up with.

Chagpar We are going to take a short break for a medical minute. Please stay tuned to hear more from my guest, Dr. Doug Brash.

Medical Minute

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Breast cancer is the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year and nearly 200,000 nationwide. But, thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with breast cancer. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing

unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital. More information is available at YaleCancerCenter.org.

Chagpar Welcome back. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Doug Brash. We are discussing skin damage and DNA repair. So, Doug, you know what I would really like to know is a little bit more about your research and how that all ties this whole concept of sun damage and skin cancer together?

Brash Well, this turned out to be a really rewarding area to study because it has let us understand what is going on in skin cancer from the quantum mechanics level all the way up to the tissue and tumor level. For most cancers, like say breast or prostate, we do not even know what the carcinogen is, but for ultraviolet light, we have a really good picture. So, one of the first things that I did early in my career, we were trying to find out what kinds of DNA damage are made by ultraviolet light in the first place, and we discovered or rediscovered one that had not been known and then we asked, okay which ones of these are causing the mutations that we suspected at that time are important for cancer. And so, we were able to do that by combining molecular biology and genetics and the biophysics, and we identified, okay which particular chemical and physical changes to the DNA caused by ultraviolet light were causing the mutations. And the mutations turned out to be really unusual. So, we said, if we ever saw those mutations in a tumor, we would be able to tell what wavelength of light, what kind of DNA damage had been made 50 years earlier when the person was out at the beach, and that actually worked.

Chagpar Are there particular mutations that you see repetitively where you can say, oh! if you have UV rays that cause this mutation at this spot, that is going to lead to skin cancer.

Brash What happens is, as I mentioned earlier that the ultraviolet light gets absorbed and it makes the T or the C's stick together, the C mutates to a T and so it is a perfectly normal base again but it is the wrong one. And that only happens if you have a T or a C next to another T or a C and now you know why that is, and that is where the damage was. So, it all makes perfect sense. So, this is what physicists love, to see some logic and so you are not just observing an effect, you are putting together, oh! here is a pathway, here is why it is working. And so then, that lead us to identify which genes had been mutated by ultraviolet light working actually with clinicians at Yale and other places who had the tumors and were interested in working on these kinds of problems. So, we identified a number of genes and then the question becomes, okay what does that gene do for a living and why did mutating it matter, why did that lead to a cancer? One of the first genes was P53, which we now know has mutated in cancers, but we did not know that then, we had to do some guessing and we got it on the fourth try as P53

for skin and it turned out to be involved in several things including allowing cells to die after ultraviolet light, which is one way of preventing a cancer. Another thing it does is change its differentiation. Another thing it does is it participates in the signal for tanning. So, the same DNA damage that can cause mutations to death is also triggering some of your safety responses.

Chagpar Which goes back to what you were talking about before about the waste paper basket and the sprinklers?

Brash Exactly. And so what is this trade-off and from an evolutionist's point of view, nature is worried about protecting you up to the age of reproduction, it is not so worried about what happens to you at age 80 and so that is why these protection mechanisms might also come with a cancer later, and are not the biggest concern nature had and that may just be what we are living with. Then, so that has gotten us up to so far 1 mutant cell, 1 mutant cell is not a problem, so it has to colonially expand into a group of cells. Well, how does that happen? And even in the cancer field, there is a hope. People tend to think about collecting genes and identifying genes that are mutated. But, that still does not solve the physiological problem of how you got from 1 mutant cell into a tumor. Well, it turns out, ultraviolet light does that too. Just mutating the cell is not enough to make it grow any faster than the surrounding cells, but it now has an advantage if you also add ultraviolet light and the mutant cell actually does better than your normal cells and so…

Chagpar In terms of replicating and growing another mutant cell?

Brash Exactly. And that turns out to be may be even more important than the mutation, if you are on the beach twice as long, you will get twice as many mutations. But, if you are accelerating proliferation of cells, you are going up 2, 4, 8, 16…

Chagpar Right, it is exponential.

Brash Right. So, it is a big problem and I think people tend not to think about physiology so much. Sunlight also inhibits your immune system, which also is not good.

Chagpar It seems very clear that you have figured out that ultraviolet light causes these mutations, makes them grow faster, gives them a competitive advantage against healthy cells and impedes your system, so that is a perfect storm for cancer, but the next question is, that is great, but once you have figured out the mechanism by which

the UV rays actually cause this mutation, what I would be really interested in is has anybody figured out a way to prevent it, like a way to maybe get into the cell and prevent the UV rays from making that T C connection to begin with?

Brash One of the nice things about having 6 or 8 things going wrong is that if you want to prevent the end process, you only have to block one of them. So, you have got 6 or 8 chances to find some place to intervene that might actually prevent the cancer. So, the oldest one of course is sunscreen and there what you are doing is either reflecting the energy if it is zinc oxide or absorbing the energy if it is one of the standard sunscreen. The concern there is where did that energy go, and is it going to heat or is it making free radicals, which it does and then we hope that does not get into your skin. So, that is the first line of defense. People have tried to put DNA repair enzymes into skin, it is not cheap but it seems to work, so that is a possibility. One thing that we are looking at is, okay, once you excited the energy in the DNA bases, can you siphon that energy off into some other molecule, it is even better dissipating its heat and that way never make the DNA damage in the first place, and so we are looking for chemicals to do that. They are precedents, we just have to find something that works in this case. And it looks like radical scavengers may also be a way to prevent some of these events from happening.

Chagpar Radical scavengers?

Brash Free radical is a molecule that has one too many or one too few electrons, and those happen a lot. So, people talk about free radicals in aging and that turned out to be important with the melanin story as well. It makes free radicals and it turns and UV turns on enzymes that make free radicals, and so it may be that blocking those work.

Chagpar And people talk about these free radical scavengers and they talk about inhibiting the nitric oxide just in case and that kind of thing, and it seems to be something that people are talking about for everything, it is the lecture of youth and prevents cancer and people are talking about these things like anti-oxide agents that can be found in nature, I mean people talk about blueberries and all kinds of things, so does that work, can you sit out on the beach and enjoy a basket full of blueberries and prevent yourself from getting skin cancer because it will take care of the free radicals, is that where we are going?

Brash I was very reluctant to get drawn into that sort of study because of exactly the hype that you hear. And, the hype to data ratio is very high and the experimental tools you have for studying it are not very strong, because all of these agents do 6 things and how do you study one of them. However, as I got dragged into this, it turns out that this probably is important and plants have figured this out, so that on the one hand

there is the anti-oxidant story and on the other hand there is energy quenching story, like how do you dissipate the energy. It turns out that what beta carotene or lycopene are doing for a living chloroplast is not really acting as an anti-oxidant, they are siphoning off this energy. So, I have realized, okay the plants are sitting out in the sun all day, they have had to deal with this problem, and so it may well be that a lot of these chemical compounds you see in plants are exactly the sort of compounds that might be needed. Now, plants are limited in what they can synthesize and maybe we in the lab can synthesize something even more clever than what plants have, but something along those lines at a quantum mechanical level, a lot of these plant compounds are cleverly designed in the way they channel energy.

Chagpar So, that is a current or a future area of research?

Brash That is what we are working on now. It is one of the two things that we are working on now. One is trying to find chemicals that will divert the energy and as far as something that you can put in a bottle for people, things that come from plants are much easier because you do not have to worry about the toxicity, they have been around for million years and people have been eating these things. The other thing we are trying to do is figure out what was your sun exposure when you are a kid, and the way we do that now is we ask whether you had a sunburn, but if there are some ways that I can take a little snip of your skin, a very small snip of your skin and tell whether you have mutations that have been sittings there for 30 years or DNA damage that has been sitting there for 30 years because even people who have mutations and say DNA repair genes or other genes that predispose the family to skin cancer, they do not all get skin cancer, you still have to be lying out in the sun and so it is important to know what that number is.

Dr. Douglas Brash is a Senior Research Scientist in Therapeutic Radiology and in Dermatology, and Clinical Professor of Therapeutic Radiology at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on WNPR, Connecticut's public media source for news and ideas.