Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and he is an expert on Myelodysplastic Syndromes. 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 can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. Tonight you will hear a conversation about melanoma with Dr. Marcus Bosenberg. Dr. Bosenberg is Associate Professor of Dermatology and of Pathology at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Marcus, maybe we can start with melanoma in general. What is it, how deadly is it, why should we care?

Bosenberg Melanoma is a form of skin cancer that accounts for about 80% of all skin cancer related deaths, so it is by far the most lethal form of skin cancer and the thing about melanoma is that if patients and people are aware of what it looks like, they can catch it early and that usually prevents the bad outcomes from melanoma. Melanomas tend to be pigmented spots on the skin, so not all pigmented spots are bad, but there are 4 characteristics that tend to make melanoma or a pigmented spot more worrying, so if the spot is asymmetric, so it does not look like it is a round circle, it is a little bit irregular, if the border looks more like the State of Maine than a circle, then that is something that might be of concern. If there are more than 2 different colors of brown, that is something else to worry about and then if it is more than 5 mm or about a quarter of an inch or the end of a pencil head, that also is something that we look at and perhaps the most important thing is if it is changing, so if the appearance of the pigmented spot evolves or changes over a month or two then it is probably a good idea to go see your primary care doctor or dermatologist to have them look at the spot.

Chagpar For our listeners, just to reiterate, you went through what we have learned in medical school as the ABCD, so asymmetry, border, color and diameter to try and give you a clue as to whether some pigmented lesion is just a freckle or whether it is something to be really concerned about.

Bosenberg Absolutely and if you keep your eye out, there are free screening sessions for patients who may not go see their doctor for this purpose, but to add to the ABCD is that the concept of change tends to be useful and many things do not change and perhaps are not as worrying and it is probably over a 2-3 month period that you would look at it.

Chagpar When we think about melanoma, like most skin cancers, we think about sun exposure, fair skinned, blonde haired, blue eyed freckled people. Is that kind of the norm or can anybody get melanoma?

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Bosenberg It turns out that anyone can get melanoma, especially on certain spots like on the feet, it turns out that people of all ethnicities or all skin types have about the same rate of melanoma on the feet. In fact, Bob Marley, the famous reggae artist died of melanoma in his 30s. However, the other spots where melanoma happens is much more common in white people and red hair is also a risk of about threefold higher, so it is not a very high risk, but for skin cancer in general and melanoma in particular but perhaps the greatest risk for melanoma is if you have more than 50 pigmented spots on your skin, that is about a 10-fold higher risk and it is hard to keep track of all those spots as well, so even if one had red hair and less spots, it would be less of a risk than having more than 50 spots. Now most people who have that many still do not get melanoma, so you should not panic, it is just probably a good idea to have a dermatologist or a primary care physician look at you for that.

Chagpar Particularly if you are fair skinned, but even if you have got pigmented lesions, maybe going and seeing your doctor once a year, is that what the recommendations are for routine skin surveillance?

Bosenberg It really depends on the person, but going in at all is usually a reasonable thing to do just to get a baseline and now-a-days with cell phones and the ability to take pictures, holding up a ruler next to a spot and taking a picture of it is not a bad idea so that you have that record and you can tell if it is changing because usually these things change so slowly that you would not really notice it otherwise, so but once a year as part of a general physical exam, would be certainly appropriate for a skin check.

Chagpar Let us talk a little bit about prevention, because we talk a lot on this show about treatment and we are going to get into some really innovative treatments for melanoma, but before we even get there, let us try and prevent melanoma, what can we do aside from staying in a cave all day without ever having any sun exposure to prevent ourselves from getting melanoma?

Bosenberg I was trained as a skin pathologist and we do not tend to have a lot of windows in our labs, so I am sort of that cave dweller that you are talking about and that is probably the best thing, although most people do not really want to do that, so one bit of advice is avoiding the hottest or most direct sun times of the day between 10 o'clock and 2 o'clock, especially in the summertime, as much as one can. That is probably one of the safer things to do. Using clothing that covers up skin like a hat for instance, I do not have a lot of hair on my head which the viewers' cannot see, but I always wear hats when I am out because that is a spot that obviously gets a lot of sun exposure and sun tan lotions are very effective at blocking UV damage, but there are some controversies about sun tan lotion in that people do not always apply it evenly

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across all of the spots that really need to be covered, for instance the tops of ears or something like that, it is not something that one typically does and you do not want to have visible sun tan lotion, most people do not, so it gives one the impression that you can stay out in the sun quite a bit longer than you might but certain parts of your body that do not have full coverage might get two or three times the amount of sun that they would get otherwise and that is a concern. Now, there is clear evidence that on the head and neck, especially of older individuals, that melanoma has a very clear relationship to sun exposure. At the other sites of the body in younger individuals, there are many studies that suggest that having bad sunburns during childhood may play a role, but that is actually still pretty controversial, it is kind of hard to prove, but I think it is pretty unequivocal that the head and neck melanomas of older individuals really have a strong sun exposure component.

Chagpar Let's just clarify for the listeners, sun tan lotion versus sun block. There are sun tan lotions that are just there to add pigment. Those do not necessarily provide protection like a sun block, so should we be looking for SPF and is there a certain number that we should be looking for? Is higher better or not over a certain point? There is a lot of controversy that we hear in the lay public about all of this.

Bosenberg There are two main types of sun blocks or sun tan lotions, one of which is a chemically based approach that tend to rub into the skin where you cannot see the lotion anymore and have this sun protection factor, the SPF numbers, between as low as 2 or 8 and as high as about 70 or so, meaning that you could stay out in the sun theoretically 70 times longer than you might without the lotion and those actually work pretty well if you measure how well they work by how much redness you get after a typical sun exposure, they will really block that quite well. Again, you might miss some spots and that is an issue. Those basically work by getting into the skin and finding a way to chemically block the sunlight from getting further into the skin than nearer to the surface but they are not really visible. The other main approach are these kinds that have usually a white sort of pasty appearance like zinc oxide based lotions and those provide even higher protection and are best used in certain areas, for instance like the tip of the nose if you have an activity where you know you are going to be out in the sun and you might have concerns about it washing off, but again, you just have to be comfortable whether it might be visible and if it is not visible for those sun blocks, there is probably not enough of it on to have an effect and they work by reflecting the sun back away from your nose, that is why it looks white on the surface.

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Chagpar So when we are buying sun block, and I realize that the summer is pretty much over now, but for the next summer should we be looking for things like higher SPF, what is this thing called PABA, when some sunscreens say it protects against UVA and UVB, does that make a difference over one or the

other? Because there is a price differential of all these sunscreens and we want to be sure that we are getting value for our money if we are buying these to prevent ourselves from getting melanoma.

Bosenberg In theory, most of the sunscreens that have a certain SPF and higher being better, would provide about the same protection, that is what they are governed against and most of the current sunscreens on the market protect against both UVA and UVB. It is thought that most of the cancer causing effects of UV is with UVB so that is the most important one to block. There are some suggestions that UVA may also play a role but it is probably a bit less than UVB, so PABA, the chemical that you mentioned was a part of sun tan lotion in the past that now typically is not included in sun tan lotions and some people have allergies to certain sun tan lotions and certain fragrances in sun tan lotions and so forth, so it is usually up to the individual to buy what their preferences is if they want something that smells like coconut or not. I think there are strong opinions on that and usually people are guided by that, but I think a dermatologist would generally recommended that the higher the SPF level is what you would want to do and that you would really want to make sure that when you apply it that you have applied enough and you have covered all the areas that are going to be exposed to sun.

Chagpar When you talked about sun block, you talked about it being a chemical, and a lot of people are really worried about chemicals that we are putting on our bodies, in our bodies, are there any dangers to these sun blocks?

Bosenberg It is hard to know because sometimes it could be a very long time before one would see that, but as far as we know with the current sun blocks and sun tan lotions, there is not anything that people have been able to tell and in fact, the thought is that they are preventing a lot more bad things from happening by preventing the skin cancers and preventing the UV damage that goes along with it, the ultraviolet light damage. One of the things that people tend to miss though is, for instance, the lower lip is not an area where one would put sunscreen but there are lip balms that are actually SPF ratings as well and it is very common for older individuals that have had a lot of sun exposure during their lifetime to have pre-cancers on their lower lip because it gets a lot of sun exposure, so there are things that you would not really think of when you are putting on lotion, that probably are not a bad idea to keep in mind it is not just the skin surfaces, it is also things like the non-hair bearing parts of the lower lip that also gets sun damaged.

Chagpar And there is clear evidence that sunscreens do actually prevent melanoma, is that right?13:06 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201004%20YCC%20
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Bosenberg In studies that are usually using model systems, you can see that there is less UV damage, less damage to the DNA of the cells and also less melanomas in those models. In people, it is harder to figure that out. One thing that we can look at in people is that there are 2 other main types of skin

cancer that happen in sun exposed skin in particular, one is called basal cell carcinoma and the other one is called squamous cell carcinoma and basal cell carcinomas by far are the most common cancer in people. There are about a million cases per year in the US and squamous cell carcinoma is about 300,000 or 400,000. In contrast, melanoma is only about 70,000. Those do not tend to be lethal but they are very strongly associated with sun damage, so you see a reduction in those cancers when you use sun tan lotions and that is a bit more clear, so I think there is pretty good evidence that melanoma is UV associated and that sun tan lotion will help, but staying out of the sun is also a good idea.

Chagpar We are going to take a break for a medical minute and after the break, we are going to talk more about how we actually treat melanomas in incidents where we actually did not prevent it to begin with. Please stay tuned to learn more information about melanoma with my guest, Dr. Marcus Bosenberg.

Medical Minute The American Cancer Society estimates that over 1500 people will be diagnosed with colorectal cancer in Connecticut alone this year. When detected early, colorectal cancer is easily treated and highly curable and as a result, it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the one at Yale and at Smilow Cancer Hospital to test innovative new treatments for colorectal cancer. Tumor gene analysis has helped improve the management of the disease by identifying patients most likely to benefit from chemotherapy and newer targeted agents resulting in a more patient-specific 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. For more information, go to yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Marcus Bosenberg. We are talking about melanoma. Right before the last segment and the break, we were talking about preventing melanoma which is one of the most deadly forms of skin cancer, but now let us switch gears a little bit and talk about how this is treated. Let's suppose that somebody maybe forgot to use sun block on a particular area of

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unexposed skin, follows the ABCDs that you talked about at the outset, and finds a lesions that is changing, goes to their dermatologist presumably, has a biopsy, it comes back melanoma, then what?

Bosenberg I will put my two cents in for what I do in this process. I am actually a skin pathologist and what happens after someone sees the dermatologist or primary care physician that performs a biopsy of a spot that they think needs to be evaluated, someone like myself will look at the tissue under the microscope

and will determine whether or not it is a melanoma and will also add some information that tends to tell the doctors about the care of the patient moving forward, whether or not it is a high-risk melanoma, and what the next steps need to be for that patient. Most melanomas are fairly thin, less than a millimeter in thickness or less than about an eighth of an inch, and that is typical for an early melanoma and this is where catching them early is a big help. If it is thicker than that, what people typically do is, there is some danger that even that small cancer which might be just about a quarter inch or half an inch across, has already spread to something called the lymph nodes, and it might go, for instance, if you had it on your hand, it would go towards the armpit and that will be the first place one would expect to see it go and so what is done is a surgeon will then map out where the cells should have gone and will take out that lymph node, it will be evaluated by a pathologist and they will determine if there seem to be any melanoma cells in that lymph node. If it is positive for those cells, they will take some more lymph nodes out to hopefully reduce any tumor that spread to that early spot. For most patients, at that point in time, they are free of disease and they are just going to a dermatologist usually every three months for the first couple of years and then maybe every six months and then every year. For the vast majority of patients, that is their course. They do not actually ever have more advanced melanoma than that and they just see a dermatologist more regularly. For some individuals, it depends on how thick the original melanoma was, they actually will have more advanced disease, so they might feel, for instance, a lump growing in their armpit or in another location and so then they will have follow-up with a doctor who will determine if the melanoma has spread. They will do radiology exams, they might put a needle into the spot that seems to be growing to see if there are melanoma cells in it or do another biopsy of that and then pathology will be involved to determine if that actually is melanoma and at that point usually the surgeons would have taken out all that they can of the tissue and the patient will go to a medical oncologist to determine what the options are and that usually is a discussion that we will have with medical oncology.

Chagpar Let's go back a little bit, it sounds like the thickness of the melanoma is really a critical feature in terms of determining how patients are treated. Are there other factors that also play a role,

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like maybe where it is on the body? You talked about Bob Marley having it on his foot, is that better or worse than somebody who has say a freckle on their face or does that make any difference at all?

Bosenberg Surprisingly, the thickness really seems to work well and that is really the main thing. Nothing really has improved on the ability to predict how patients are going to do aside from whether or not the surface of the melanoma is open or ulcerated, and that tends to make the melanomas behave a little bit worse than they would otherwise, and more recently, we have learned a lot

about the genetic changes that drive melanoma, so there was hope that with that new information we might have the ability to tell which patients would do really well and which ones will not. That has not really impacted care yet in terms of predicting how patients are going to do based on those changes. There is still some possibility that it will eventually, it just has not happened yet, but some of those genetic changes actually are tested for to determine whether or not the patient qualifies for certain types of therapy because they only work in patients with certain changes.

Chagpar We are going to get back to that in a minute, but just to clarify for the listeners as well, we are talking about the thickness of a melanoma as in how far down in the skin it goes, you really are not talking about the surface area that you can see, so if you had a massive melanoma that was 6 cm in diameter but it barely went through the skin, that might not be as bad as if you had a 6 mm melanoma that went down through all of the layers of the skin, is that right?

Bosenberg That is absolutely correct and that is sort of surprising. It does not seem to make sense that that is the case, but when you follow enough patients that have had those larger surface area melanomas but they are not very deep, then you notice that they do pretty well in terms of their survival and not having recurrences, and the thickness that we are talking about here, the range is from less than 1 mm to the highest thickness that we stop at which is 4 mm, which is less than a 0.4 of an inch thick, so that is already considered thick for a melanoma. Again, the idea of when there is something flat that is changing and not necessarily growing out you really want to catch it when it is flat rather than when it is growing out because that already has a pretty noticeably worse effect on survival.

Chagpar I think the take home message here is that it is really not what you can see on the surface, it is how deep it is, which is only something that people in the pathology lab can tell, so if you see something that is changing, go and get a check-up because you do not know how thick it is until you have it under the microscope.

Bosenberg That is absolutely right, sometimes they stick out from the surface a little bit and that can be helpful if they are growing out like that, but not all things sticking out from the surface and are

23:03 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%201004%20YCC%20Answers%20-%20Dr%20Bosenberg_234078_5.mp3pigmented are bad, in fact, the vast majority are not. It is the ones that are changing and that stick out or are thicker that are more worrisome.

Chagpar I tell all my patients that there are only two people who can tell you anything for sure, God and the pathologist, so if you do not know if something is changing or you do not know what it is, you need to get it checked out so that a pathologist can tell you. Let us move onto therapies. You talked a little bit about genetic changes and the fact that while this may not predict prognosis, it may actually have a role to play in what kind of treatment you are eligible for.

Talk a little bit about different kinds of medical treatment, we talked a little bit about surgery, which seems fairly simple in the sense that you take out the melanoma and you check lymph nodes, but there is a lot of movement going on in the field in terms of how we can target certain pathways, certain things about melanomas or even other cancers that are really novel. Do you want to talk a little bit about that?

Bosenberg This is really an exciting time in melanoma. For a very long time, for almost 40 years, until about 5 years ago, there was no new therapy in melanoma that actually made patients live longer, so that was a very long time where you are using things that maybe helped 5% of patients, if that, and not even for a very long time and a little over 10 years ago, some of the first genetics of melanoma were being worked out and there was a gene that is called BRAF that was identified as being changed in about half of all melanoma and the nice thing about this particular gene which makes a protein is that you could make drugs against it and so several companies moved pretty quickly and in almost record time, about 7 or 8 years, it went from the discovery of a gene involving cancer to having an FDA approved drug for, which is about half the time that it might typically take and part of the reason was that when they got the drugs that worked on this particular gene or protein it was so obvious that it was working that it made the approval part easy and so patients that have this certain mutation in the BRAF gene respond to the BRAF inhibitor and it was really one of the triumphs in modern medicine in trying to have this concept of personalized medicine where you have the patient's tumor evaluated on a more molecular level and you have a drug that is really set up to target that particular genetic change and between 50 and even more percent of patients that had that drug would have their tumor stop growing and even shrink by more than 30% and would have what they call disease free survival advantage, they would not have their melanoma recur or progress for about a year. One of the challenges with this therapy is that it tends to have patients eventually get resistant to the therapy and perhaps live on average about 12 to 18 months longer than they would have otherwise, but the vast majority of patients eventually do recur, so additional drugs were added in that pathway and it works a little bit better than that now, but it is still a major problem in melanoma treatment for the BRAF and related inhibitors, that resistance emerges in a large number of cases.

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Chagpar And so if resistance emerges then what?

Bosenberg That was really a tough question about 4 years ago. During that time, coincidentally another set of therapies was being developed and these were therapies that made the immune system work more actively in anyone who takes the therapies and one of the discoveries was that if you make your immune system more active, or remove the brakes on the immune system, all of a sudden you are able to sometimes fight cancer including melanoma, so melanoma was really at the forefront of the development of these immune based

therapies and even about 10 or 12 years ago there was one that was based on blocking a gene called CTLA4 and 5 to 10% of patients who had this blocking therapy to this gene had dramatic responses, so it is clear that you could, even see in some cases with a large melanoma tumor, shrink it away and the patients would live for 5 or 10 years, so they live out long enough, which is really pretty spectacular. It was still a minority though, only about 10 or 15% seem to have these long and durable responses but what was nice about it was that there were patients that seemed to be cured, or had really long survival based on the new therapy that was given, so that was very exciting and to some extent based on the success and the concept of removing the brakes on the immune system, additional genes were targeted including something called PD1 and something that interacts with PD1 called PDL1 and several companies have made drugs to block PD1 function, making the immune system work better and again, before the clinical trial, one could not know how well this would work in people, but it is pretty clear that probably now 30% or more of melanoma patients have long-term survivals with just that one drug and even from several different companies that are making a drug like it, all seem to have very good survival and based on that, now several other cancer types are using this to treat their patients with lung cancer, prostate cancer, even in breast cancer treatment where there are lots of very good treatments for most breast cancer patients, but some need to have something else.

Dr. Marcus Bosenberg is Associate Professor of Dermatology and Pathology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next 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.