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## An Update on Melanoma

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*Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is an oncologist who specializes in pain and palliative care. If you would like to join the discussion you can contact the doctors directly at [canceranswers@yale.edu](mailto:canceranswers@yale.edu), or the phone number is 1-888-234-4YCC. This evening Ken speaks with two members of the Yale Cancer Center Melanoma Program, Dr. Stephan Ariyan is a Clinical Professor of Surgery at Yale School of Medicine, Associate Chief of Surgery at Yale New Haven Hospital and Director of the Melanoma Program. Dr. Harriet Kluger is an Assistant Professor of Medicine specializing in the Treatment of Melanoma.*

Miller I want to start out with some very basic questions that I think people are wondering. What is a mole and what is melanoma, and how are they different from each other?

Ariyan A mole is an area of the skin that has particular cell types. There are two types of moles, one where we're born with pigment in it, which is an unusual one, called congenital nevi. This was based on old thinking that we did not develop moles until after we were born, so it got the name congenital nevus. In point of fact, the rest of the moles actually developed pigmentation later on after we are born, usually within months in response to hormones. It turns out that we all have moles the day we are born. The pigment is just not produced until later on. Those moles are all benign. The question is whether or not they have the potential of turning into a malignancy, in which case we have a melanoma.

Miller Why is there the transition from normal mole, or nevus, to melanoma, what happens?

Kluger We think that the biggest insult to these moles is sun exposure, that the radiation from the sun can cause some of these genes to change or undergo what we call mutations. These mutations then allow these cells within the mole to grow uncontrollably, and that is what makes them cancerous or malignant. There are also some people who are born with certain predispositions to having their moles turn malignant, and sometimes that happens without sun exposure. We also want to point out that not all melanomas happen in sun-exposed areas; there definitely are other environmental insults that occur other than the sun, but by far the sun is the worst culprit of causing melanoma.

Miller There are different types of skin cancer that people can develop. Where do they arise from? Do they all come from pigmented cells or are they coming from other parts of the skin?

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- Ariyan            There are three important cell types that develop into cancers. They are all in the very first layer of the skin. The first are called basal. The basal cells are at the bottom part, which is why they are called basal, and make up about 75% of all skin cancers, again related to the sun. The second most common are called squamous cell cancers, also in that layer of the skin. They are more maturation cells that evolve from the basal cells as they come closer to the surface. They are much flatter cells and make up 15% of all the skin cancers. The third type, which are the least common, are the melanomas and they are the pigment producing cells that are also in that first layer, but at the bottom part right alongside where the basal cells are. The important thing is that it is very rare to have basal cells, or squamous cells, which make up 95% of all the cancers, spread to either the lymph glands or other organs, whereas other melanomas can do that, which is why we are much more attentive to them.
- Miller            Who is at the highest risk of developing melanoma, is there a certain age, group or sex?
- Kluger            Men have a higher risk for developing melanoma and it can happen in any age group. In fact, it is the most common malignancy in men in their 20s and 30s. People with fair skin, red hair and blue eyes, are more predisposed, as are certain families that carry genes that predispose them. We do not know for sure whether there are any particular ethnic groups that are more likely to get it but definitely it is more common among fairer ethnic group such as the Irish.
- Miller            As Harriet has mentioned, anyone who is Irish, with fair skin in particular, should pay attention to sun exposure and try to protect themselves. It's winter now so it is a little less of an issue, but still a problem. I want to ask you some truth or myth.
- Ariyan            Okay.
- Miller            Is it just fair skinned people who develop melanoma?
- Kluger            No. In fact, we have African-American patients and Hispanic patients, so certainly not just people with fair skin get skin cancer.
- Miller            Next one, Stephan let me ask you this one. Truth or myth, melanoma is always a black pigmented lesion.
- Ariyan            That is truthful in the majority of cases. The majority are pigment producing cells, although we do have some melanomas that have absolutely no pigment production. Sometimes the diagnosis of this is one

that could be missed by the patient and dermatologists doing a routine screening may look at it and notice that it is different and does not know what it is. There are a variety of other things that it could look like if it does not have pigment. They will do a biopsy and then it is confirmed on histologic or microscopic examination that this is a melanoma that does not produce pigment.

- Miller Let me ask you the third one. Truth or myth, melanomas sometimes regress and disappear spontaneously.
- Kluger That is true, and in fact, of the patients who present with what we call metastatic disease, where it has already spread from the skin, 20% of the time we do not find the primary site because it has regressed on its own.
- Miller How could that be? Looking at other types of cancers, that does not happen. We do not see that in lung cancer. What are your ideas in terms of why that happens in melanoma?
- Kluger More than any other cancer, with the exception perhaps of kidney cancer, melanoma is an immunogenic cancer, so when it occurs it actually activates the immune system to act against ones own body. It is almost like an autoimmune phenomenon and sometimes you see patients come in with vitiligo because their immune system is acting against the skin and they may have melanomas that have regressed.
- Miller That is fascinating.
- Ariyan To make that an analogy to a home and family and children, the cancer cells are most protected when they are in the entire cluster of where it started and cells always have a propensity of leaving that cluster, which is like children leaving home too soon. If they leave too soon, they are in a very hostile environment and they are not likely to survive. What can happen is a melanoma cell leaves the cluster, and in the vast majority of cases, it will be destroyed, but occasionally, it may convert genetically, immunologically, and change of surface protein so that the body's immune system does not identify it and leaves it alone, but does attack the primary home and destroys it. We can't find the original, but we find this clone of cells that has changed its characteristic and allows itself to grow so we never find out which home they came from.
- Miller That is a very good analogy. Steve, let me ask you, when you see a patient and you are doing a skin survey, what catches your eye. Teach us a little bit about what people should look for and what doctors should look for.

Ariyan Most often surgeons do not do the skin screening. The dermatologists depend on the patient coming to see them frequently, depending on the amount of skin changes and damage they have. The most important thing are the ABCD's of the skin. This is basically change in appearance, change in diameter and change in color. The most crucial change is when there is a mole with pigment that suddenly begins to lose pigment. Invariably, that is a very suspicious lesion because that probably indicates an immune response destroying the melanoma cells, causing the loss of pigment. Although it may look like it is getting better, it may actually be showing that it has more malignant potential. Having said that, the latest addition is the E, which is evolution, or change. Change is the most important thing that we have to keep in mind. I have to say, there are many times when the patient will come and say that they think there is something wrong with a mole and it may look perfectly normal. I have learned over the years that when the patient says something is wrong, even if I do not see it, it's probably safer to take it out because sometimes a patient can get a sense, whether it is an itching or irritation, and occasionally we have found a malignancy where it did not look like a malignancy. On the other hand, once every two or three years I will see something that I am absolutely convinced is a malignant transformation. But after a biopsy it turns out to be a benign lesion like hemangioma that has some irritation and scarring.

Miller If a patient does have melanoma, and they come to see a dermatologist, what would you do in terms of surgery?

Ariyan Did you say if they have the diagnosis?

Miller If they have the diagnosis.

Ariyan Once the diagnosis is made, we will begin a decision tree. There are many forks in the road we have to go down. The first thing we look at is how deep the melanoma is, not the diameter but how deep into the skin, microscopic amounts of deep. The reason for this is because the deeper the melanoma is, the higher the probability that those cells that left home have a potential of changing character and surviving elsewhere. Therefore, the thicker the melanoma, the higher the probability there could be some cells in the lymph glands or other organs. If a melanoma is deeper, we will begin to look and examine the patient for regional lymph glands to see if it is enlarged. We will begin to do an evaluation of other organs such as the lung and liver with a chest x-ray and a blood test. This is what establishes the staging system and helps decide what should be done next.

Miller Harriet, let me ask you, who would you consider to be at a higher risk of

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developing a recurrence of melanoma, what kind of features do you look for in regards to that?

Kluger The depth of invasion into the skin, as Steve just said, whether this is ulceration, or not on the actual melanoma, that is a really important sign because when the skin is ulcerated above the melanoma, it is a sign of aggression of the melanoma cells and their ability to invade and destroy structures around them. Involvement of lymph nodes, or spread to a lymph node, is a very poor prognostic feature. There are other factors such as the patient's age and gender, but those are less important than the presence or absence of ulceration, the depth and the involvement of the lymph glands.

Miller If you have a patient who you think is at high risk of recurrence, what can you do for them to reduce the risk of the cancer coming back?

Ariyan If we feel an enlarged lymph gland in a patient who is at higher risk of a thick melanoma, the probability that there is cancer in the lymph gland is 80%. It is not 100%, even though the lymph gland is enlarged, because sometimes the lymph gland will enlarge in response to its immunity against the melanoma. Sometimes we take it out and find no cancer. But if we do find cancer in the lymph glands, we take out the entire group. The analogy is thinking about the lymph gland as filters for the body against outside attacks such as allergens, poison ivy, insect bites, bacteria, scratches or from cancers that are immunogenic. These are the areas that trap the cells, identify what the protein is so it can go ahead and attack it. The fact that somebody has involvement in the lymph gland does not mean we can't cure them because we can get rid of the lymph glands and we can rid of the cancers in the lymph glands. Involvement of the lymph glands does not cause, we do not believe, other involvement. It is an indicator that there could be something somewhere else, and again, thinking of the children that left the home as special forces that invaded enemy army territory, the lymph glands are the headquarters. This is where the immune system is and if we find some enemy cancer cells in the territory, we can take them out, we can arrest them. It always tells us that if one or two were capable of getting into headquarters and surviving unidentified, there is the possibility that there are other sisters and brothers lying somewhere else in the body that we cannot identify. It tells us that we have to be more vigilant when we do the next line of test for identification.

Miller In other types of cancers such as breast cancer, we give chemotherapy or hormonal therapy after a woman has surgery. What do you do for melanoma?

Kluger You are referring to what we called adjuvant therapy. That means therapy to decrease the chance of the cancer coming back. For melanoma there is one FDA approved therapy for the circumstances called high-dose interferon. It is not all that well tolerated so we cannot give it to older patients, but that is the only thing that we have available right now. There are a couple of other therapies that we are experimenting with, but it is a little early to talk about those at this point.

Miller How does the interferon work, do we know?

Kluger We are not sure whether it works by direct kill or by activating the immune system, but we do know that in patients who developed immune activity while on the interferon, such as thyroid problems or vitiligo, tend to do better.

Miller Interesting.

Kluger There clearly is an immune component to the interferon therapy.

Miller This fits well with what you were telling us about melanoma and how it sometimes regresses by itself with some kind of immune phenomenon. Let me ask you about vaccines, what is going on there?

Kluger People use the term "vaccine" very broadly; sometimes people call it immune therapy. I am not sure exactly what people are referring to when they use the word vaccine. There are a number of immune based therapies that we have now in the clinic, most of them are used for metastatic disease patients, in another words, patients who have identifiable children who have escaped the home, to use Dr. Ariyan's analogy, so we can try to activate the immune system to attack those children. We have at least three or four therapies that we are using now, some of them are more experimental than others. One has been FDA approved called high dose interleukin 2. We have been using it for a number of years and there are a couple of others that will most likely be FDA approved over the next couple of years.

Miller We would like to remind you to e-mail your questions to us at [yalecanceranswers@yale.edu](mailto:yalecanceranswers@yale.edu). We are going to take a short break for a medical minute. Please stay tuned to learn more information about melanoma with Dr. Stephan Ariyan and Dr. Harriet Kluger from the Yale Cancer Center.

*Medical Minute*

*There are over 10 million cancer survivors in the US and the number*

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*keeps growing. Now completing treatment 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 can be difficult and cancer survivors may face other long-term 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 cancers such as the Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute. You can find more information at [www.yalecancercenter.org](http://www.yalecancercenter.org). You are listening to the WNPR Health Forum from Connecticut Public Radio.*

Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am here with Dr. Stephan Ariyan and Dr. Harriet Kluger, discussing latest treatment options for patients with melanoma. We had an email question from Mike who lives in Hartford. He says. "My father had melanoma and so did my aunt, am I at an increased risk?" I think what he is asking here is if there is a family tendency to developing melanoma.

Ariyan I think we need to give a little definition here. There is a difference between hereditary and familial. Melanomas are not hereditary. If we look at hereditary diseases and take 10 people out of the particular disease and follow them for 10 generations, based on the probability of that heredity, you can predict in the 10th generation how many of the offspring, or what percentage, should have the particular disorder. We do not see that with melanoma; however, if you take 10 patients with melanoma and you follow them for 10 generations, you may see a number of families that have absolutely no links or any association with melanoma again. Then over there in a corner we may see one family where some siblings, cousins and others develop melanomas and it is a spotty thing, that is what we call familial, which is what happens with melanoma. My recommendation to the patient is that if there is a family history, you should begin to think of this cluster. If a patient tells me that their father, aunt, or cousin had melanoma and a sibling had it, that makes me think of a familial group. We then ask that the children be examined to see what kind of moles they have and if they are suspicious looking moles. Other than that, if there has been no history, it is probably not a hereditary thing.

Miller We also had an e-mail from Marsha who lives in Springfield. Her question is, "Is melanoma more common in people from the North East?"

Ariyan I think it would be interesting to look at the incidence of new cases in Connecticut. For example, I am looking at the data that I used in one of my lectures, the data from last year shows we had 690 new cases of

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melanoma in the State of Connecticut. When you compare that to New York, they have 3200, and compared to Nevada it is only 540. So, the question is, are we at higher risk. To determine this you have to look at the population of the state and if you change the number to risks per hundred thousand people in the state, the 690 in Connecticut equals the same risk, maybe a little bit higher, than New York which is 3200 and California which is 5000. The incidences come to somewhere around 15 to 19 incidences per hundred thousand people. On the other hand, when you look at the states that have the greatest amount of sun such as Arizona, Nevada, and Florida, Florida has 4600 new cases and Nevada only has 540 cases. Their incidence is about the same. It is about 23 to 26 per hundred thousand, much higher than California, New York, and Connecticut.

Miller Again the point that it is sun related.

Ariyan It is definitely related to sun. The closer we live to the equator the higher the incidence within the population per hundred thousand.

Kluger The country that has the most melanoma in the world is Australia because there are a lot of fair people with Irish origin or English origin living close to the equator. I just want to emphasize again we have a relatively high incidence in Connecticut and that might have to do with lifestyle, being on the water, patient population, and lots of different possibilities.

Miller We talked a little before the program about the ozone layer, how does that relate to sun exposure and risks? What changes the ozone layer for example?

Kluger The ozone layer is getting thinner in certain areas because of fumes and chemicals and things like that. The ozone layer does filter the sunrays, so when the layer is thin, more rays can penetrate. Another geographical factor that we have to take in to account, that is not all that pertinent for us in Connecticut, is the elevation above sea level; the higher the elevation, the more radiation, even if it is not that close to the equator.

Miller Let's move on to a different topic that has to do with patients where the melanoma has come back, let's say it has come back to a different part of the body. What kind of treatment do we have to offer those patients?

Ariyan We need to separate these two categories, those that are within an area of the body that we can reach and take care of, and those that are in more remote areas of the body where the treatment may be a little more difficult or a higher risk for the patient. Clearly, if there is any local recurrence that we can take care of surgically, we remove it. But it raises the

question, if it is possible for these to have survived the patient's immune system, what is the likelihood that there are others that are also hiding? That leads into the staging system again and doing CAT scans and PET scans. One of the things that we get sometimes is a recurrence in an extremity such as the arm or leg, and then we get a second recurrence or third recurrence. It is important to note that in our experience for 10% of the patients who get a recurrence, it is their only recurrence, so we're not as aggressive on the first recurrence, say a single recurrence in the skin within a few inches of where the original site was. We take it out and in 10% of patients that is it, nothing else ever shows up. But in 90% of patients this is the hallmark of something new. It is like dandelions, if you see one dandelion it is easy to just take it out. If you see two more a week later, you can take those out and if you see five more you can take those out. Now the first did not cause the second, the second did not cause the third, they just grew at different intervals. These recurrences of cells were in the area at the time of original treatment. They lay dormant, and they could lie dormant for as much as 15 to 20 years. But when you get more than one, if you get a second crop or third crop, it tells us that there are probably going to be more. If you leave it alone, you are going to have a yellow lawn. So the next question is, while you are taking some of these out, can you prevent the others from growing? This is where the systemic treatment comes in and Harriet will discuss this in a minute.

Kluger We have a number of systemic therapies that we offer. There are two that have been FDA approved; one is the high dose interleukin 2 we can only give to patients that are very strong, robust and in perfect health other than the melanoma. It is an inpatient treatment that is not easy to do, but it induces durable responses. We are always afraid of using the term "cure", but there are patients who were treated with this therapy in the 1980s and have yet to have the melanoma come back. It is sort of a high-risk therapy, but if it works, it yields high outcomes.

Miller Sure.

Kluger Chemotherapy often times works in higher percentages, in maybe 15% to 20% of patients, but the duration of it working is much, much shorter. We have these immune therapies that we are very excited about. In a couple of them we have seen some dramatic responses that sometimes last for years.

Miller I have heard of something called limb perfusion, and Steve you talked about how there have been regional recurrences, and Harriet you talked about systemic, let's focus on regional first. What is limb perfusion?

Ariyan Let me give you an example of a patient who has multiple recurrences in

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the extremities and all the tests show that there is nothing elsewhere in the body; it is only in the arm or the leg. We can give systemic treatment to the whole body which would cause side effects from the drug, or another option is to give a high dose of chemotherapy to just the arm or leg. We use a surgical procedure and put a tourniquet around the arm or leg, put catheters into the main artery and vein, perfuse it with a high dose of drug and get very little to the rest of the body so there are no side effects.

Miller Which is a terrific way to deliver the medicine. Harriet, what are some of the new therapies?

Kluger There are two that are FDA approved and there is another one that is probably going to be approved in the next year or two. It is an antibody that we give intravenously once every three weeks and it activates the immune system. We give it for three weeks, four times, and if the patient is responding, we do it once every 12 weeks. It is actually, for patients who respond well to it, a very nice and easy thing to do. We have a bunch of other therapies which we call biological therapies, sometimes they activate the immune cells, sometimes we use them to actually attack the melanoma cells and sometimes they do both. I think that what we are going to see over the next 10 to 20 years with melanoma is that we will have therapies that work for 10% of the patients, and there will be another therapy that works for a different 10% of patients. Our problem now is predicting which patient is going to respond to what therapy so that we can tailor the therapy and personalize it, similar to what we do in breast cancer where some patients receive hormone therapy. Hopefully we will have a menu of therapies that we will be able to give and personalize the medicine, but we still have a lot of work to do to get to that point.

Miller Keep working because it sounds like you are making a lot of progress and that is wonderful. I want to thank Dr. Stephan Ariyan and Dr. Harriet Kluger for joining us on Yale Cancer Center Answers. Steve and Harriet, thanks for being with us.

Ariyan It was a pleasure being here.

Miller Until next week, this is Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week.

*If you have questions, comments or would like to subscribe to our Podcast go to [www.yalecancercenter.org](http://www.yalecancercenter.org) where you will also find transcripts of past broadcast in written form. Next week, Ken speaks with Dr. Mary Jane Minkin about cancer and fertility.*