

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 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 in, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week is a conversation on colorectal cancer awareness month with Dr. Howard Hochster. Dr. Hochster is Professor of Medical Oncology at Yale School of Medicine and here is Dr. Steven Gore.

Gore I cannot believe it has been a year, I think we did a show last year for colorectal awareness month and I feel like I have been pretty aware of my colorectal parts most of the year.

Hochster I guess you have gotten your screening.

Gore Well, I am 58 years old, truth be known.

Hochster Okay.

Gore And I should have had...

Hochster At least one by now.

Gore I had my colonoscopy about 3 weeks after my 50th birthday and this was something I was looking forward to in a certain way.

Hochster That is the key, we recommend, we being the American Cancer Society, the American Gastroenterological Association and other organizations too, to begin colorectal cancer screening at the age of 50 for people at normal risk.

Gore And what is normal versus abnormal risk?

Hochster If you are normal risk, you basically do not have a family history of colorectal cancer including a first-degree relative.

Gore Okay.

Hochster However, if your parent or brother or sister had colorectal cancer, you should get your first

2:05 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

colonoscopy 10 years earlier than the age at which they were diagnosed.

Gore So 10 years earlier than their age.

Hochster Yes.

Hochster For most people and maybe late 30s on rare occasions, but we know that colorectal cancer develops from polyps to cancer over a number of years and if we remove polyps, that are these adenomatous polyps, the kind of ones that are premalignant, you can prevent colorectal cancer. There are a number of trials where people have gotten colonoscopies for screening and it has lowered mortality, the number of people who have died from colorectal cancer, over 20 years or 30 years of follow-up, so this is really a strategy that can lower your risk of colorectal cancer. We know that it does take a few years, and that is why we recommend starting 10 years earlier. It takes a few years to go from the polyp to the cancer stage.

Gore I know that when I had my screening 8 years ago which was normal, I was happy to say, they gave me a 10-year return which I thought was generous and now all of a sudden it is 2 years until then and I am already thinking about it.

Hochster First of all, there are about 150,000 cases a year of colorectal cancer in the United States and the incidence has come down a little bit with better screening and we can continue to improve that, so colorectal cancer can be prevented to a large extent with screening and screening colonoscopy. The test itself is not that bad. I mean people do not like getting cleaned out the night before, which is part of it because you want your gastroenterologist to be able to see what is going on in there, so you have to have a pretty clean colon, but it is not so bad, today they generally use propofol for anesthesia and you kind of go to sleep, you wake up, you are fine.

Gore Yeah, that was my experience. Howard, one thing that I think many of our patients worry about is many people will have some kind of bleeding occasionally from hemorrhoids or other things that we think of as pretty local and not worrisome, but we do not want to tell people necessarily not to worry about rectal bleeding, so what is your take on that? Should people who are having any kind of bleeding get earlier or interval screening or just talk to their doctor about that?

Hochster I would say most of the time people present with colorectal cancer with no symptoms and that is the idea of screening, there tends to be a long interval with no symptoms. Some people with rectal tumors especially, can have bleeding, so if you have persistent rectal bleeding that continues or comes back, more than a couple times, you should see your physician about it.

5:09 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

Gore But a one-time smear on your toilet paper?

Hochster It is probably not that worrisome.

Gore Probably not worrisome, got it, so what is new in colon cancer since the last time we talked? Have we come up with any new treatments, any new cures, anything exciting?

Hochster I would say the most interesting thing that is happening in colorectal cancer today is better understanding of the biology, so we know that many patients, let us say 15% of people with stage II cancer will have a kind of colon cancer that arises in the setting of certain gene abnormalities. We call them mismatch repair or enzyme deficiency, those are the spellcheckers of DNA. When you and I learned about DNA, we thought it was just this double helix thing that never changed, but actually DNA is quite active, it is a very plastic system and it is always reproducing, the DNA is opening and closing and sometimes you get a spelling error in there, a bad base, an abnormal based, so the spellchecker is going to fix that, but if you have an inherited deficiency in the spellcheckers or you acquire one, there are certain conditions where people can acquire these through what we call gene silencing, then you are more likely to get colon cancer. The good news is those colon cancers tend to be largely cured by surgery alone. They are moreso, even though you get it, it is not a very effective colon cancer, it does not tend to spread, so the cure rate with surgery is very high for these mismatch repair enzyme deficiency cancers, but if you do have metastatic disease, these are the ones that we can now use immunotherapy drugs for and there are a number of trials. We are opening one this week looking at one of the new immunotherapy antibodies pembrolizumab compared to chemotherapy for first line treatment of these what we call MMR or MSI high colon cancers, the ones that have a lot of abnormal gene behavior. They are the ones that we can use immunotherapy for and then we are also finding and we are studying to understand a little better that different parts of the colon may give rise to different biologic types of colon cancer, right sided and left sided. This is a new area of research that people are beginning to understand better.

Gore And why is that?

Hochster Well it may have to do with some of the same factors about the genes that are expressed more or less when you get the colon cancers.

Gore I see, it is not that the right side of the colon is so different from the left side of the colon?

Hochster Well genetically, it is apparently different enough and actually embryologically, they evolve a little bit differently and the colon kind of fuses together in the middle.

8:10 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

Gore You are really challenging my basic knowledge.

Hochster Yeah, I know, I forgot that stuff too.

Gore So with this mismatch repair gene abnormality, some of these sound like if they are genetic they would be in the setting of a familial colon cancer?

Hochster Yes, that is correct. There is a common familial colon cancer which is called Lynch syndrome or hereditary nonpolyposis colon cancer, a very bad

name because it makes it sound like you do not have polyps but you do have polyps but you just do not have what we call polyposis which means 1000s of polyps, you only have dozens of polyps, so it is a very bad name, but that is what it is called. HNPCC, or Lynch syndrome, are families that pass down bad genes for the spellchecker and the mismatch repair enzyme and in each person if your parent has it, you have a 50-50 chance of inheriting Lynch syndrome. The thing about Lynch syndrome is, it most commonly causes colon cancer but there are other cancers that can arise because of the same gene repair deficiency, so people get the second most common endometrial cancer of the uterus, so there are other cancers and people need to be observed carefully in a high risk clinic. We do have a high risk clinic where people like this can be monitored for not only colon cancer but other cancers.

Gore How would you know if you are in this high risk group, would you have a family history?

Hochster Usually there will be several family members that have colon cancer or endometrial cancer and people will know if they have a strong family history. Gore You said there is also a sporadic mutation, so you would not have that history.

Hochster No, for those we just check it today.

Gore You mean you actually check all the tumors to see if they have that mutation?

Hochster Yes, it has now become standard recommendation of the pathology organizations and in our practice here for a number of years already but a national recommendation that all colon cancers be checked for this microsatellite instability or this gene defect or repression with the gene errors because it has major therapeutic implications today. For the early stages, it means less chemo; for the later stages, it may mean some immunotherapy.

10:53 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

Gore Would this immunotherapy be more active in this particular kind of colon cancer compared to others, if I am understanding you correctly?

Hochster There are a number of theories. We have not proven it entirely but the main theory is that because you cannot repair the DNA and the DNA kind of falls apart in an abnormal way, you get many more abnormal genes and these produce foreign proteins on the cell called antigens, so these foreign antigens that are a result of a high number of mutations are what brings in the immune reaction. Most of colon cancer seems to be protected against that. We do not find a lot of immune cells infiltrating colon cancers except this type and so that makes it a little bit different from certain kinds of lung cancers where the immunotherapies worked in melanoma where there seems to be a higher gene mutation rate.

Gore Are you saying that in this particular colon cancer variant, when you actually look at the tissue, you can see the immune system already infiltrating into the tumor sometimes?

Hochster Well there are more of the immune cells and lymphocytes which are some of your favorite cells that are actually found in these right-sided colon cancer tumors that tend to have the microsatellite instability, so the pathologist can see that sometimes. I do not think for 100 years anybody understood what they were about but now we are beginning to have a greater appreciation for it.

Gore But apparently they are not doing a good enough job or the cancer would not be there and would not be growing.

Hochster Well as in all these cancers that are susceptible to immunotherapy, the tumor takes a normal stop sign, a signal to the immune cell that says, hey, I am normal, do not attack me because in most cases the immune cells will kill foreign objects in the body, bacteria, viruses and so forth, so you have normal ways of telling the immune system, hey lay off and the tumors kind of adopt them and they like put up 100s of these stop signs so the immune cells cannot kill them. The new such antibodies such as pembrolizumab, nivolumab and atezolizumab, they come in and block that stop sign, they kind of cover it so the immune cells can get back to work.

Gore Fascinating, let's plan to pick that up after the break, but right now, we are going to need to take a short break for a medical minute.

Medical Minute 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, non-invasive 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

13:52 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

age 40 or earlier if they have risk factors associated with breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer center such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to make innovative new treatments available to patients. 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 at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am talking with my guest tonight Dr. Howard Hochster about colorectal

cancer. Howard, before the break, you were explaining to me and to the audience how in this particular subset of cancer with microsatellite instability, is that what it is called?

Hochster Yes.

Gore Or Lynch syndrome and you gave a few other names for it, the pathologist had observed that there are immune cells that infiltrate the tumor, nobody really understood what that was about and now you find that some of these new drugs which activate the patients autoimmune system turn out to be particularly active in this cancer, can you tell me what kind of studies have been done that showed that? Were they particular trials in the subset or were there trials in all comers of all different kinds of colon cancer where these patients sort of stuck out as good responders to the therapy?

Hochster That is a great question and the answer is both, there have been a number of trials in colon cancer the same way that we did in melanoma and lung. In general, colon cancer is not very susceptible to this kind of immunotherapy when the drugs are used by themselves.

Gore Okay.

Hochster I think we are beginning to experiment and try to understand more if we can in combination with other drugs that may induce more of an immune response but you do not get a very robust immune response with most colon cancer. However, with the subset, the MSI high group, again that is only about 8% of metastatic colon cancers, so there are not a lot of people out there who have this, it is a minority, but it is an important minority because it kind of gives us a clue about the biology and how to use immunotherapy better, so the current trials are looking more at if you give chemotherapy with these drugs, if you give radiation or embolization with the drug, if you give certain other kinds of

17:03 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

targeted therapies, start to kill some of the cells first, will you be able to then turn on the immune system a little better.

Gore And how robust are the responses when you have seen them?

Hochster Well for the patients who do have this kind of MSI situation in some of the other trials, these are people who had a very high response rate in that more than 50 or 60% had real tumor shrinkage and many patients have been on these drugs for years with the immunotherapy which is really fairly nontoxic. I mean there are some immune side effects that can be significant but in general, because they are antibodies, they are not like chemotherapy, they have no acute side effects, no nausea, vomiting, hair loss, lowering the white blood cells, things that we tend to associate normally with cancer and chemotherapy. Gore Some antibodies have symptoms associated with infusions, is that not the case here,

chills and fevers?Hochster Yeah, once in a while you get something like that, but it is very unlike chemotherapy.

Gore Have any of these patients been cured? Or you are controlling them for a long period of time, it sounds like?

Hochster I think it is hard to know if some are cured at this stage just because there has not been long enough follow up.Gore But the tumors visibly go away, completely?

Hochster Sometimes, yes.Gore That is pretty exciting.Hochster I mean all of this has been in the last 2 years and there is very little long term evidence of how well it is going to work, but it is certainly a lot less toxic than standard treatment and people seem to tolerate it for much longer.

Gore Tell me about the new trial that you are alluding to in previously untreated patients with this kind of cancer, you said they are being randomized to chemotherapy versus this or chemotherapy plus?

18:58 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

Hochster No, the patients will have a 50-50 chance of getting the immunotherapy drug or standard chemotherapy regimen; however, if they do get the standard chemotherapy regimen and it is not working, then they can get the drug as a crossover, so you would eventually get immunotherapy.

Gore So that makes it a more palatable trial for the patients whom I am guessing that most of them would rather have immunotherapy?

Hochster Well I think if we knew it worked as well as chemotherapy we would rather give it but that is still too soon to know.

Gore I see.

Hochster There have been handfuls of patients who have done very well with this but no real large trial that is comparative yet.

Gore I am wondering from a patient perspective, if you have to be a risk taker to be enthusiastic about this or whether the stuff itself is so hopeful that most patients would prefer to go on it.

Hochster I think that for people who have that kind of biology, they have this MSI high situation, they should really look into these kinds of trials for 2 reasons: First of all, we have already seen for melanoma and lung cancer, these randomized trials have come out uniformly in favor of the immunotherapy. Second, we have got a handful of people who have responded really well in an unprecedented way for immunotherapy and third of all, you will not be able to get these drugs very easily for colon cancer even if you have this kind because they are not approved today for colon cancer, so it would be what we call off-label use and it is hard to get insurance to pay for that, so if you go into one of these trials, you will either get immunotherapy first or second.

Gore Unless the chemotherapy happens to work really well?

Hochster Yes.

Gore That is pretty good too.

Hochster Yeah, that would be good too.

Gore It is interesting, and is super exciting for this population of colon cancer patients but you have pointed out that this is less than a 10% subset, so that leaves 90% of people still wanting something new, what is going on for those people?

21:10 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

Hochster As we kind of peel away the layers of understanding on the biology, there are other subsets that we are beginning to understand better and developing more specific therapies for, so we have been focused a lot on another 5-6% population that have something called BRAF mutations and the drugs that have been used for these tumors that have the BRAF mutation need to be paired up with antibodies against something called EGFR but now we are seeing that that works very well, so we have a number of trials going on to help prove that this is an effective therapy and end up getting these drugs approved for colon cancer as well as other cancers, so those are another group that are BRAF mutated and we have already learned that if you have another protein called RAS, if you have a RAS mutation, there are certain drugs that will not work, we are getting better at understanding the biology and giving you the drugs that will work better for your kind of tumor.

Gore So called personalized medicine?

Hochster Right.

Gore RAS is one of the bigger players in colon cancer, right?

Hochster Yes.

Gore I think a lot of colon cancers have RAS mutations but there are no real drugs that target RAS per se yet in an effective way?

Hochster Right, that is true. RAS is considered the un-druggable target. It really is a tough nut to crack because it is a little bit different than some of the other molecules that we found inhibitors for and it works in a kind of different pathway.

Gore The drugs that were targeted for RAS some time ago, I remember tipifarnib, lonafarnib, none of them was a bit hit, right? Hochster Not for solid tumors. Gore They were not great for liquid tumors either. They have some activity.

Hochster Right, they did not directly inhibit the molecule. They kind of attack this anchoring part of the molecule so it would fall off the membrane but they

just did not work that well.

Gore So lots more work to do. These molecular tests that you highlighted identifying certain important features both positive predictors of response and perhaps in the case of RAS negative predictors of

23:44 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

response to certain treatments, are they routinely done by all pathology labs, I mean if you have a Joe Schmo local community hospital, should you assume that these tests are being done?

Hochster Well I would say that the hospitals around Connecticut are very high quality generally speaking.

Gore Nothing Joe Schmo about them.

Hochster No and I think the physicians and pathologists understand this and it is done most of the time, I would say, usually oncologists will request some of these tests to be done specifically once they see the patient, but it has become pretty routine for people treating colon cancer to request these RAS studies because they have some significant therapeutic implications for the kind of treatment paradigm, so I think that is being done fairly routinely. The other thing that we have been looking at that is not specifically a targeted therapy but kind of is an interesting approach, is we have worked with a company that originated with some of the pharmacology scientists here at Yale looking at Chinese herbs and one of the things about herbal products is that they tend to vary a lot because one season the plant will have a certain amount of chemical and the next year they may have 20 or 30% less, so they have taken mixtures of four traditional Chinese medical herbs and standardized it into a very medicinal kind of preparation, so you know what you are getting and they have characterized it in a number of biologic systems that shows it really influences in inflammation, so one area that has come out is that some of the chemotherapy drugs that are used in colon cancer cause a lot of side effects of diarrhea and we are doing a study sponsored by the National Cancer Institute looking at some of these what might be considered as alternative medicines but in this case, it is really a medical preparation to see if it reduces diarrhea, so we are working with a couple of institutions around the country and the NCI, the National Cancer Institute, to investigate this Chinese herbal preparation, so that is also in the clinical trial here for second line therapy of colon cancer, if you get first line chemotherapy and that is a kind of thing that is applicable to everybody.

Gore So it is like getting regular chemotherapy drugs in conjunction with these herbal preparations to try to reduce the toxicity?

Hochster Right.

Gore And is everybody getting the herbal drugs?

Hochster No this is also a randomized study where some people are getting it and some are not so that we can compare.

Gore So the ones who are getting are getting a placebo?

26:52 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

Hochster They are getting pills, but they are placebo pills.

Gore So, we do not know, gotcha.

Hochster We do not know either.

Gore But there is no downside because they are getting the same chemotherapy, they would anyway.

Hochster That is right.

Gore So it sounds like it would be reasonable for patients who are seeing their oncologists who is planning their therapy to just ask, was it measured for mutations and do I have it?

Hochster Yes, the RAS mutations are the most important for standard therapy with certain anti-epidermal growth factor antibodies, so those are called cetuximab and panitumumab, so you need to know if you have normal RAS or mutated RAS to decide if you should give those drugs, so that should be determined for sure and then we want to measure RAF in most and BRAF in most.

Gore That is 5% one you mentioned.

Hochster Right because there are specific drugs and then many people are doing a wider gene panel, 150 or a couple of 100 gene profile which are done in commercial labs, we have an excellent gene profiling and tumor profiling laboratory here at Yale that does an excellent job in looking at the tumors. Gore And that is to look for other targets you have not thought about?

Hochster Well, they are rare targets, there are drugs that are approved for different tumors, not necessarily for colon cancer but it might only come up a couple of times out of a 100, we can get those drugs on trials, there is this match program from the NCI and a few other things where we can get targeted therapies for people who have unusual tumors with these targets, so that again comes under this kind of off-label use but we have ways to get the drug, so that is important.

Gore It sounds like it is really very hopeful time in colon cancer.

Hochster And again, just to come back to the beginning, I do want to encourage people, it is colorectal cancer awareness month, which means every person who is 50 years or older if you have not had a screening colonoscopy you should really go for one, please see your gastroenterologist. It is not only screening

29:03 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200327%20YCC%20Answers%20-%20Dr%20Hochster_249456_5.mp3

but it can prevent colon cancer from developing by removing these premalignant polyps and that is the key thing, it is not just diagnostic but it is actually curative and preventative.

Dr. Howard Hochster is a Professor of Medical Oncology 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.