Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. 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. March is colorectal cancer awareness month and this week we conclude our series of conversations about colorectal cancer with Dr. Howard Hochster. Dr. Hochster is Professor of Medicine and Medical Oncology, Associate Director for Clinical Sciences and Clinical Program Leader of the Gastrointestinal Cancers Program at Yale School of Medicine. Here is Dr. Steven Gore.

Gore Colorectal cancer awareness to me means, make sure you get your colonoscopy.

Hochster Yes, that is probably the most important thing. Unlike many other cancers where screening can help diagnose, coloscopy is both diagnostic and therapeutic and what I mean by that is when you have a colonoscopy, if you have a polyp, and especially for the polyps that we call adenomas which are premalignant, they can be removed very easily by the endoscopist, by the gastroenterologist and that actually prevents colon cancer. There are many long-term studies now showing that colonoscopy with removal of adenomatous polyps improves survival from colon cancer. People who do not get colon cancer never have to worry about surgery later, they never have to worry about chemotherapy, radiation, all the things we do when people have more advanced disease, so it is diagnostic and it is preventative, much more so than mammography which just tells you to go have another biopsy or something. We know that this will prevent colon cancer from happening, so colorectal cancer is largely preventable if everybody goes for screening colonoscopy.

Gore That sounds so great, why is it then that everybody isn't running out and getting theirs done?

Hochster It is not pleasant to contemplate colonoscopy. It is not pleasant to prepare for your colonoscopy and people do not like the idea, even though the procedure itself is not too bad, mostly today people get it with some anesthesia or sedation and you just lay down and go to sleep, wake up half an hour or 45 minutes later.

Gore What about those virtual colonoscopies that we heard about a couple of years ago where people were getting some fancy CT scans?

Hochster CAT scanners are getting to be much more accurate in terms of measuring small things and so they can actually see polyps by doing special views of the colon and they are actual software that makes it look like you are undergoing a colonoscopy, so it is kind of a drive look, but the problem with virtual

colonoscopy, or what they call CT colonography, that is the official name, is that a lot of times you have material debris sticking to the wall of the colon if you are not cleaned out perfectly and that looks like a polyp, so it is not as accurate and also, if you do see polyps, you still have to

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get a colonoscopy to get them removed, so it was not approved in the end by the US Preventative Services Taskforce, so it is not completely covered by all insurance or Medicare. It may get there yet, but for a lot of people, they still have to go for a colonoscopy afterwards.

Gore And is the preparation for the virtual colonoscopy the same as for regular colonoscopy?

Hochster Yes, you really need a really good clean out.

Gore So there really is no advantage from the uncomfortable perspective.

Hochster I am not sure that it is so uncomfortable today. You are supposed to drink liquids for a day and not eat solid food and then the evening before you usually take a laxative, so I do not think for most people it is terribly uncomfortable, but it is a little bit unpleasant.

Gore But I am saying it is not any less.

Hochster It is not any less. It may even be more.

Gore Right, because you are out of it, so you wake up and it is done.

Hochster Right, and when they use the scope and they do a real colonoscopy, they can wash the walls and they can get a better look. Gore Who is recommended to get a colonoscopy, are we talking about 50-year olds?

Hochster The official recommendations of the American Gastroenterological Association (AGA) and the American Cancer Society is that for people at normal risk, they should go for a screening colonoscopy beginning at the age of 50 and the reason for 50 is that that is when we begin to see a higher incidence of colorectal cancer in the general population. For African-Americans, there is a little bit of an earlier onset, so for African-Americans of normal risk, standard risk, it is recommended they start their first screening colonoscopy at age 45. Once you have a colonoscopy, especially if you do not have polyps, then you do not have to have it done for at least another five years.

Gore And who is considered to be at high risk?

Hochster The people who are at normal risk are everybody in the population that do not have a family history of some colon problem or colon cancer in a first-degree relative, in a parent or in a brother or sister. For those people, they are recommended to begin screening colonoscopy at 10 years prior to the age of the diagnosis of the first-degree relative, so if your parent had colon cancer at

the age of 50, you should get your first screening colonoscopy at the age of 40. And then there are some

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family syndromes where you may start even earlier, familial adenomatous polyposis requires earlier onset screening, that is a very rare condition, Lynch syndrome, what we call today, HNPCC, hereditary nonpolyposis colon cancer, it is a really bad name, sorry.

Gore All those names.

Hochster A called Lynch syndrome, HNPCC, probably requires starting screening earlier because the people who have this are predisposed to developing polyps and early onset colon cancer.

Gore How would I know if I had one of those?

Hochster Usually it is by your family history.

Gore So it is more than one first degree relative?

Hochster In HNPCC, usually it is or it is in every generation somebody gets colon cancer because it is a 50-50 chance, it is a dominant inheritance.

Gore I can imagine that it still requires a smart physician to put two and two together and see a pattern in the family to start doing a genetic work-up right?

Hochster Yes, I in Lynch syndrome, or HNPCC, there is a defect in something we call mismatch repair enzymes. They are like a spell checker for DNA. Because DNA is constantly replicating and sometimes it gets a bad base in there. It is like a spelling error, so the spellchecker enzymes go around and fix the spelling errors and that seems to be particularly important for the lining of the colon possibly because your colon is exposed to so many different chemicals and noxious substances, so when you have an inherited deficit in one of these spellchecker enzymes, then you tend to get polyps and colon cancer in an earlier age, so basically you have to have at least two generations with one person having it at least under age 50 and in addition to colon cancer, there are certain other kinds of urologic cancers, endometrial cancers that are seen commonly in people who have Lynch syndrome so if that sounds like something in your family where people in every generation seem to have one of these kinds of cancer, it may be worthwhile asking your doctor about it or seeing a clinical genetics person. It is very easy to test for today.

Gore But it still requires that you either have a concern about your history or your primary care doc is taking a really thorough family history, which I have to admit that not all of us do all the time in the hurried environment that we are finding ourselves in. But with a good family history, you might look at it and say, well there is a lot of cancer in your family, a lot of colon cancer in your family, so the next step is to send them to a cancer geneticist?

Hochster Yeah, it is a lot of colon cancer and also early onset, usually earlier than age 50.9:58 into mp3 file http://medicine.yale.edu/cancer/podcasts/2015%200322%20YCC%20Answers%20-%20Dr%20Hochster.mp3

Gore Got it.

Hochster There are genetics programs here at Smilow and we have genetic counseling, so they will tell you about the syndrome and do the appropriate test. Usually it is either a blood test or scraping some cells off your cheek, a buccal smear, and they can define whether it is something that runs in the family, if you test somebody who actually has the illness, or if you have not had it, if you are at risk, if you inherited the enzyme deficiency.

Gore Let's say that your family is known to have this syndrome, or suspected to have this syndrome, and you get tested at a young age and you do not, then can you go back to normal risk screening?

Hochster Yes, if you did not inherit the gene mutation, so your mismatch repair or spellchecker enzyme genes are normal, then you are at normal risk, the same as everybody else in the world.

Gore You dodged the bullet.

Hochster Yeah.

Gore That is great, so that is just a blood test or a swab?

Hochster Yes.

Gore That seems pretty innocuous, and so in these people who have these family syndromes and are receiving early screening, is the maintenance or therapy then just to take out the polyps as they come along or are people at risk of having a colectomy or colon resection removal?

Hochster It depends on how big they are and how many people have them. If a lot are coming up over the years, then sometimes we do surgery.

Gore What about people who have things like ulcerative colitis or inflammatory bowel diseases? They can sometimes be at risk for cancers, is that right?

Hochster People who have active inflammatory bowel disease, mainly ulcerative colitis, for more than 10 years on treatment, they are at high risk for developing colon cancer and may need surgery as a preventative measure, but usually those people are under very close surveillance by a gastroenterologist, so they do not really fall into this general screening.

Gore So they are done separately. I remember when I was a medical student those patients used to have prophylactic colon resections.

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Hochster That is done sometimes today too. Often it is not the whole colon and rectum but they leave a little bit of some of the rectum to be more functional and that can be watched very closely with a little procedure that is less than a colonoscopy.

Gore With all this new development of new targeted drugs and likely targeted drugs, is there any movement in these people with these genetic defects with the spellcheckers for therapeutic interventions, specifically?

Hochster There are a few, for the people who have this Lynch syndrome, mismatch repair enzyme, they actually have an unusual biology where they are more likely to get colon cancer but they are less likely to have a bad colon cancer, so they actually need less treatment. We can talk about that a little bit more after the break.

Gore Dr. Hochster reminds me that we are going to need to take a break for a medical minute. Please stay tuned to learn more information about colorectal cancer with Dr. Howard Hochster.

Medical Minute It is estimated that over 200,000 men in the United States will be diagnosed with prostate cancer this year with almost 3000 of these diagnoses here in Connecticut. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. 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 test innovative new treatments for prostate cancer. The Artemis machine is a new technology being used at Smilow that enables targeted biopsies to be performed as opposed to removing multiple cores from the prostate for examination which may not be necessary. 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 joined today by my guest Dr. Howard Hochster. We are discussing colorectal cancer to end our series for Colorectal Cancer Awareness Month which is March, and is it March every year?

Hochster Every year.Gore So every year, I can wear my purple, which is the color correct?

Hochster Purple ribbon.

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Gore It is not representative of anything that we produce in our colon, for example.

Hochster I do not think so. Gore Howard, I know that you have got a very exciting colorectal cancer research program here at Yale Cancer Center and I am wondering if there is anything you would like to tell us about the clinical trials that you are involved with?

Hochster There are a few things, we were just talking before the medical minute about inherited colon cancer with this Lynch syndrome.

Gore You said people need less treatment sometimes, not more.

Hochster Yes, the amazing thing about when you have this mismatch repair enzyme deficiency, there is a mutation in the spellchecker and you are more predisposed to get cancer, but if you do get cancer, it is skewed more towards early stage and also it does not tend to metastasize as much, it tends to stay treatable with surgery, so we tend to treat those people less than your average colon cancer patient at stage II or stage III. I would say Lynch syndrome is around 10% of colon cancer and in addition, there is another few percent of people who have sporadic deficiencies in these spellchecker enzymes, so they get it and they are the first one and it is not in their family, so it is a minority, but it can happen. These people have a condition that we call microsatellite instability which means your DNA tends to fall into little pieces much more easily and that seems to be the reason that cancers do not tend to be as bad as in people who have your garden variety colon cancer, so if they have stage II, usually we do not have to give chemotherapy and in stage III, it is still a question. If it does turn out that people have this kind of microsatellite instability and then get metastatic colon cancer, so advanced colorectal cancer, we actually have a trial for them now using the new immunotherapy drugs which you may have heard about which seem to work for some diseases like melanoma and lung cancer quite a bit, but not too well for your normal colon cancer. People that have this microsatellite instability type of colon cancer, because they have a lot of DNA defects and mutations, tend to attract the immune cells more to their kind of colon cancer. This is known for a long time by the pathologist. They say these tumors tend to be more on the right side which is the first part of the colon and not the left side and they tend to see a lot of lymphocytic infiltrate which means the immune cells are getting into the tumor and they seem to be responding to these drugs like nivolumab and pembrolizumab that are the anti PDL-1 drugs that are the kind of new immunotherapies that are taking the brakes off the immune system.

Gore It is not bad enough that you have got these syndromes that have like 5000 syllables and now you are treating them with medications that have about 5000 syllables.

Hochster Yeah, I know. The key thing is that these immune therapies have an antibody that kind of takes the brakes off the immune system, like we used to

think for the last 20 years, the immune system does not work because if your immune system worked properly, you probably would not get

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cancer, so let us see if we can stimulate the immune system, so we gave all kinds of immunostimulator drugs like interferon and other things that sometimes worked a little bit but this is a whole new ballgame. We found that the tumors have a protein that kind of masks them, that puts on the brakes of the immune system, so an antibody that gets rid of that protein makes the immune system work better and really helps us treat these cancers better, so we are seeing that in people with colon cancer from Lynch syndrome, we have a trial open now using an antiangiogenesis drug, bevacizumab or Avastin.

Gore Angiogenesis.

Hochster That is the process by which the cancer cells track blood vessels, so we block the blood vessels and we block the immune system with a drug called MPDL3280 at the same time and it seems to work pretty well together.

Gore Bevacizumab with this other PDL-1 drug.

Hochster Yes, the anti-PDL-1 drug.

Gore And this is just for Lynch syndrome that is advanced?

Hochster Lynch syndrome or other microsatellites, exactly.

Gore So you are turning on the immune system and you are starving the tumor at the same time.

Hochster Yes, this is the drug that reduces the blood vessels and starts the tumor creating more what we call antigens as they are proteins that tell the immune system I am bad, come attack me, so we are kind of increasing the targets for the immune system and taking the brakes off the immune system at the same time.

Gore Are you worried that by decreasing the vasculature and the blood vessels to the tumor, you might not get the immune cells in?

Hochster It is a concern, but so far we have not done a comparative trial of the drug alone with or without the bevacizumab, the Avastin, but so far it looks like it seems to be helping more than harming.

Gore So this still is a smallish subset?

Hochster Right.

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Gore By the way, I just wanted to ask you, do you think that this sort of immune attraction or stimulation, I guess it is not really stimulation but attraction that

they have noticed in these patient's, is one of the reasons why it is presenting at earlier stages and less likely to spread? Do you think that there is some activating system?

Hochster It is possible, but I think the other part of what you said is the cancer at times has its intrinsic Achilles' heel, so even though you get a cancer, it is a wimpy cancer.

Gore Not to say that you should not be screened for it, but take care of it aggressively because wimpy cancers can still kill.

Hochster Right.

Gore What about for the patients who do not have this microsatellite instability?

Hochster The other signaling proteins that we screen for today in colorectal cancer are basically the RAS family.

Gore So by signaling proteins you mean proteins that turn on the proliferation or growth of the tumor, is that right?

Hochster Right, so we know that when cancers, normal cells too, but in cancer, the system seems to be revved up even more, there are signals that tell the cell to grow and then within the cell there are a whole series of protein that kind of come in a series or a cascade that eventually result in the cell being divided and growing. So there are a number of points along the way where you can block that and then some of these proteins if they do not have an activating mutation, it is like having a street light that is stuck on the green, a green light never turns red, so it is stuck in the on position or it is like your light switch, you cannot turn it off. So the light is on all the time, it just tells the cell grow, grow, and grow.

Gore It cannot turn off the faucet, which I hate. Drip, drip, it is terrible.

Hochster Yeah, like the faucet. So we are interested in two of those proteins, specifically in colon cancer, that have clinical implications today. We are looking at many of the signaling molecules as kind of new therapies, but there are a couple of things we are looking at in clinical trials. First of all, there is something called a RAF mutation, a BRAF mutation, and that happens in about 4% to 5% of all colon cancer. We have a drug for that that can block the BRAF signaling protein and it did not work that well by itself in colon cancer. It is approved for melanoma but for colon cancer by itself it was not that good so we are combining it now with another antibody that blocks the signaling pathway in another place and that would be an anti-epidermal growth factor antibody. So basically we are putting the antibody together with this BRAF inhibitor and it seems to be

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working quite well. We have some clinical trials for patients who have a BRAF

mutation and have gotten other chemotherapy but it is not working. We have an investigational trial combining these drugs which are not approved for colon cancer.

Gore That sounds like kind of a small minority.

Hochster Right that is a subset too.

Gore A small subset.

Hochster The other thing is the people with the RAS mutation, RAS comes in a couple different ways, people have been talking about KRAS for a long time, we have NRAS also, but when you have these RAS mutations, it again tends to tell the cell to grow. It is kind of like the faucet is turned on and leaky, but we do not have a good way to turn off RAS. RAS is one of these molecules that nobody has come up with a good drug to block it because it is different than the other signaling proteins, it has got a different biology, so what we know about those is that the RAS mutations can tell us which drugs that can work or cannot work, so the patients who have RAS mutations, we do not tend to use these anti-epidermal growth actor antibodies and that is about half the patients with colon cancer. So today we kind of look at colon cancer as RAS mutated or RAS normal, or wild type, and then we have different treatment paradigms depending on the RAS status.

Gore Whether they are Rastafarians or not?

Hochster Not exactly. RAS wild type or RAS mutated.

Gore You are no fun.

Hochster I also do not have dreads.

Gore For those who have never seen Dr. Hochster, it would be interesting for him to have dreads. So how do people get these mutations, how do they know if they have these mutations or not in their tumors?

Hochster Unlike the Lynch syndrome we were talking about where they can test your normal DNA, that is called germline DNA, we are not interested in it for this. We are interested in looking at your tumor DNA. Your tumor DNA is different than your normal DNA because it has accumulated these mutations that made the cells go bad. So once you get your tumor biopsied or removed, we take some of the cells, extract the DNA, and then we sequence it and we look for either specific mutations by looking at probes for those mutations or we do whole exome sequencing where we look at all the DNA patterns in your whole DNA of the tumor, all 19,000 genes.

27:45 into mp3 file http://medicine.yale.edu/cancer/podcasts/2015%200322%20YCC%20Answers%20-%20Dr%20Hochster.mp3Gore Wow! So it sounds like the take home messages for Colon Cancer Awareness Month are, make sure you get screened earlier, or later depending on your status, and if you have the cancer removed, make sure it is studied for some of these very informative mutations.

Hochster And not only informative, but mutations that have therapeutic implications. We have trials that can address some of these issues.

Dr. Howard Hochster is a Professor of Medicine and Medical Oncology, Associate Director for Clinical Sciences and Clinical Program Leader of the Gastrointestinal Cancer Program 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 format 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.