

Yale CANCER CENTER *answers*

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Colorectal Cancer Awareness Month: Screening Tools

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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 begin our series on colorectal cancer with guest host Dr. Howard Hochster. Dr. Hochster is Professor of Medicine in Medical Oncology, Associate Director for Clinical Sciences and Clinical Program Leader of the Gastrointestinal Cancer Program at Yale School of Medicine. Dr. Hochster will be talking with Dr. James Farrell. Dr. Farrell is Associate Professor of Medicine in Digestive Diseases and Director of the Yale Center for Pancreatic Diseases. Here is Dr. Howard Hochster.

Hochster Tell me a little bit about what you do for colon cancer and why it is important for people to have a colonoscopy?

Farrell I am primarily a gastroenterologist and within the field of gastroenterology, I am actually an interventional gastroenterologist or interventional endoscopist and I form a part of a multidisciplinary team that includes oncologists, radiation oncologists and radiologists, that are involved in the management of patients with both colon cancer as well as at risk for the development of colon cancer. There are approximately around 130 to 140,000 cases of colon cancer every year. It is up there at about the second or third most common cancer both diagnosed as well as death from cancer amongst men and women in the United States and about 50,000 of those individuals ultimately die from cancer. However, there has been significant improvement in mortality from colon cancer over the last 20 years or so, some of that has to do with improved treatments from the world of oncology and radiation oncology, but actually a good chunk of it, I believe, has to do with screening for colon cancer, and we know a lot about the molecular biology, the pathology and natural history of colon cancer. The colon is about 5 feet long. It is kind of the last part of your gastrointestinal tract; if you are going from above down, we start with the esophagus just after the mouth, we head on into the stomach, then you have a large 20 foot organ called the small intestine where fortunately not too much happens, but then you get into the colon and that is obviously where colon cancer arises from. We talk about colon cancer, but we also talk about rectal cancer. They are similar in terms of their pathogenesis and development, but the rectum, where rectal cancer arises, is really the last 10 to 15 cm of the colon and you will hear people talk about them differently in terms of the work up, be it the surgical management or radiology.

Hochster So that is the last 7 inches?

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- Farrell Yes, that is the last 7 inches or so of the colon, but when it comes down to development of cancer either in the colon or the rectum, we believe that the pathogenesis and risk factors are somewhat similar.
- Hochster What you said before was that the incidence of colon cancer has gone down and the mortality, meaning fewer people are getting colon cancer and fewer people are dying of it every year, and that is mainly due to screening colonoscopy, that seems to be the main driver, is that correct?
- Farrell I believe it is probably one of the major drivers, but I think you also have to say there have been a lot of great developments in the world of medical oncology and radiation oncology as well as improved surgical technique for patients with colorectal cancer and that has definitely made an improvement.
- Hochster We have definitely made progress in treatment, but the incidence really is a result of what?
- Farrell Screening.
- Hochster Right, colonoscopies that can remove polyps before they become malignant.
- Farrell Both colon cancer prevention as well as colon cancer early detection, and we know for a fact that colon cancer arises from what are called polyps and specifically, polyps known as adenomatous polyps. These are normal growths of tissue that occur anywhere in the colon and it takes probably anywhere from about 10-15 years or so for an abnormality to develop through the stages of polyp into colon cancer. It is somewhere in that range of years and so that means that we have an opportunity to intervene in that period of time to try and identify these polyps, these adenomatous precancerous polyps and remove them before they even become a cancer and that is really where the strength of colonoscopy comes in, so colonoscopy is a screening modality. It is a type of endoscope with a light and camera at the end of it. It is a very flexible endoscope. It can make its way easily around those 5 feet of colon that we talked about. It can actually even make it into the small bowel if need be. Typically, the patients who are undergoing a colonoscopy are deeply sedated with a medication such as propofol, for example, that allows them to recover quickly after the procedure and one of the beauties of colonoscopy or direct endoscopy is the ability to see these polyps. These are not cancers, but these are the precancerous polyps that can range in any size, anywhere from a couple of millimeters up to larger 5, 6, 7 cm in fact and they can be biopsied to diagnose, that means a piece of tissue can be taken through the colonoscope, a little piece of tissue is taken off using a small biopsy forceps and sent to a pathologist to confirm that in fact it is an adenomatous polyp and then for certain types of polyps that are precancerous, we have the ability to actually remove those polyps completely and initially we were very good at removing small 1 cm or 2 cm polyps and now we have developed techniques and technologies to allow us to remove 5 cm, 6 cm polyps that in former times we would have sent to surgery for direct surgical resection, so these are advances that have been going on in the world of both screening colonoscopy and colonoscopy to allow us to do these things.

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- Hochster In general, you want 0.5 cm or 1 cm polyps or centimeter plus, somewhere between 0.5 to an inch in size and if you remove those, you really prevent people from getting colon cancer.
- Farrell Correct.
- Hochster And how do we know that?
- Farrell There is long term data from screening colonoscopy trials that have shown that people enrolled in active screening colonoscopy trials have a decreased incidence of developing colon cancer over time and obviously individuals, for example, who have had previous colon cancer or previous colon polyps when they are followed up with interval colonoscopy after those events, they also have a decreased incidence of developing colon cancer or even colon polyps, so there is good strong data to support that colonoscopy works.
- Hochster We have studies that are 10-15 years old where people got randomized to either colonoscopy or standard care and people with colonoscopy had fewer incidences of colon cancer and better survival, colon cancer specific survival, based on having undergone this screening procedure?
- Farrell Correct.
- Hochster So even though it is something that people are a little squeamish about and nobody wants to think about the colon or preparation for colonoscopy or even having a colonoscopy, colon cancer can be prevented by colonoscopy, by removal of this premalignant lesion, these adenomas.
- Farrell Absolutely, in year the 2015, we have a prevention technique to prevent the development of colon cancer and compared to a lot of the other cancers that we deal with within the GI tract, for example, esophageal and stomach and pancreatic, we just do not have the same sort of strong screening tools that are available for colon cancer and so it is certainly our recommendation, the recommendation of the medical community at large, that people of a certain age and a certain risk profile undergo screening colonoscopy.
- Hochster Who are those people?
- Farrell It all depends on your risk for developing colon cancer and it breaks down into several groups. The vast majority of people are the groups who are at average risk, so these typically are people over the age of 50, but if you are African-American, we would say, over the age of 45, because at those ages, the incidence of colon cancer takes off and our goal is to get in at those ages and identify those individuals who are otherwise asymptomatic and who do not have any strong family history of colon cancer. Now, if we take a step back, obviously if there are individuals who have symptoms that could be attributed to colon cancer, then those need to be worked up, you need to see your physician. You need to see a gastroenterologist to get those evaluated. They include

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things such as rectal bleeding, alteration of stool habit, such as development of constipation, development of what we call obstructive symptoms whereby there may be a blockage or something similar in the large bowel.

Hochster So if bowel movements change, they are thinner, they are more liquid, is that something to get checked out?

Farrell Correct, if there is something new, that was not there, that is prolonged and there is no good explanation and obviously as you said issues related to bleeding, those would be things that the patient needs to go and see a physician for to get properly evaluated, so those are a separate group of individuals. The larger group of people are the people who are completely asymptomatic and do not have any family history of colon cancer whatsoever, as I said, for most individuals, it is the age of 50 and above and for African-Americans, I would say around the age of 45 and above.

Hochster So basically, every person who is 50 or older if you are Caucasian, or 45 or older if you are African-American should really go for a screening colonoscopy.

Farrell Correct.

Hochster Do you have any idea what percentage of people actually do this?

Farrell It is certainly not 100% but I think it is certainly getting better. There is more awareness of it. It is probably in the region of 40 to 50% of people or maybe even lower in certain communities.

Hochster It must be with doctors where it is lower because everytime I talk about this, I ask people to raise their hand if they are 50 or older and keep their hand up if they have had a screening colonoscopy and usually it is about 10%.

Farrell It certainly has gotten better, I think people are more aware of it as a cancer screening tool. There is a public perception issue of what it entails, and I think there is also a lot of confusion of what is available to patients and for a long time physicians were recommending a variety of different studies, you could have a colonoscopy, you could have a partial colonoscopy, you could just have your stool checked. Now we are basically saying for prevention of colon cancer, a standard colonoscopy that examines the entire colon is really the way to go. For people who do not have access to it or are a bit squeamish about it there are alternatives and they include things as sigmoidoscopy which is a very limited examination. There are also radiology studies such as CT colonography and there are also what we describe as less invasive studies, such as examining the stool for blood and now even DNA, but they are not really as solid as colon prevention tools for example a colonoscopy, so the number one recommendation is still for a full colonoscopy.

Hochster So the goal of the colonoscopy is to look for these adenomas and find them and you said it takes about 10 years going from when the cell starts to behave badly to becoming a cancer, so the

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adenoma is this kind of premalignant situation. What actually happens to the cells, do they kind of pile up and make a little stalk like thing?

Farrell They actually go through a variety of different mechanisms and they have a variety of different features that we are now more familiar with. The classic development of an adenoma or precancerous lesion has been something that resembles a polyp on the stalk, so a bulge with a very narrow neck that attaches it to the colon wall and that grows over time as the abnormal cells accumulate; but, unfortunately what we have also noticed is that a variety of these adenomatous lesions develop in a very flat like manner that spread out along the colon wall and we have become aware of that because initially they were not recognized partly because of the technology, partly because a colonoscopy does require the patient to really clean out their colon to have a nice clean lining so we can see and also understanding that there might be different mechanisms and routes for developing these different polyps, so there are different forms that a gastroenterologist is basically now trained to recognize and we do ensure that our patients coming in for colonoscopy really have adequate preparation. We also ensure that the gastroenterologists who are performing these procedures are aware of the need for good preparation of closely looking, of optimizing the image, so not only can they see these large polyps but they can also see these very flat lesions that sometimes are quite difficult to pick up.

Hochster We know stuff about the biology of this, right? There are certain DNA mutations that lead to polyps and then eventually lead cells to become even more badly behaved which we call cancer, so we will come back to that after this medical minute. We are going to take a short break for a medical minute. Please stay tuned to learn more information about colon cancer with today's guest, Dr. James Farrell.

*Medical
Minute*

Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven. The Smilow Cancer Genetics and Prevention Program is comprised of an interdisciplinary team that includes geneticists, genetic counselors, physicians and nurses who work together with the goal of providing cancer risk assessment and taking steps to prevent the development of cancer. 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.

Hochster Welcome back to Yale Cancer Center Answers. This is Dr. Howard Hochster and I am joined tonight by my guest, Dr. James Farrell, and we are discussing colon cancer. James, we were just talking about DNA mutations leading to adenomas or these polyps and then eventually to cancer over a long time period. What do we know about that?

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- Farrell One of the great stories in scientific breakthroughs and understanding has been in the world of the understanding of colon cancer pathogenesis and the work of Bert Vogelstein and Kenneth Kinzler who worked at the steps involved in the molecular development of colon cancer. There are things such as oncogenes which are genes that ultimately will develop cancers and things called tumor suppressor genes that prevent the development of cancers and as cancers evolve that is really the progression or the activation of an oncogene and the inactivation of the tumor suppressor gene. There is a variety of these genes that are being worked out and identified within colon cancer, one of them, called the APC gene, adenomatous polyposis coli gene, is one of the major activators and is a tumor suppressor gene found in colon cancer and then a variety of other genetic abnormalities develop over time including mutations in p53, KRAS mutations, also SMAD4 genes. There has also been work done on understanding in the TGF beta receptor genes that have been involved.
- Hochster It sounds like a lot of letters.
- Farrell It is a lot of letters and it just shows that there are a lot of different types of soup involved here and everybody's tumor has a certain degree of heterogeneity, but there is a certain consistency that occurs in certain subgroups, so for example, about 1% of all colorectal cancers are related to an inherited gene, the APC gene. The entity that evolves out of that is called familial adenomatous polyposis and so that is a very straight forward clear understanding of how colon cancer develops in that cord of individuals. There is a variety of other genes involved in DNA repair, for example, when we are all replicating our cells inside us, we have incredibly efficient mechanisms for picking up the smallest defects in our DNA and repairing them. When those repair mechanisms are faulty, then unfortunately abnormal cells develop and that is one mechanism by which a certain subgroup of colon cancers, particularly the HNPCC or the nonpolyposis colon cancers develop, but a lot of work has been done and it has lead to the development of genetic tests, both blood tests as well as some stool studies but also it impacts ultimately areas of treatment as well and risk stratification.
- Hochster Those are two examples of inherited risk factors for colon cancer, APC and mismatch repair enzyme deficiency, colon cancers, but in general, we know that there is kind of a series of DNA mistakes that happen leading to first adenomas and then over the decade, that is useful information in helping us understand the biology.
- Farrell Correct, in terms of the sequence it occurs as well as the use for those tests in terms of diagnostic tests that might be useful to try to identify when a polyp is present and when a cancer is present for example.
- Hochster So basically, you take this long camera tube and put it in the rectum and look at the whole colon; tell us a little bit about what you actually do during a colonoscopy and what preparation is involved?
- Farrell As we talked about earlier on, the vast majority of people who are presenting for screening colonoscopy are otherwise healthy individuals in their 50s who either talked to their physician

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about the need for it or their physician has talked to them about the need for it and the next step involves them being referred to a gastroenterologist who would be the expert performing the colonoscopy procedure, typically the gastroenterologist would see the individual as an outpatient, talk to them about the type of procedure, the risks of the procedure and the benefits of the procedure. We have talked a lot about the benefits of the procedure here today. There are very small risks associated with this procedure as there are with any medical procedure that anybody undertakes. The major risks that we are concerned about with this procedure are actually risks related to the sedation involved so that the patient can be comfortable during this procedure. More and more gastroenterologists are involving the use of what is called a monitored anesthesia using propofol which is a medication that will allow the patient to sleep comfortably through the procedure and wake up very restfully afterwards and go about their world.

Hochster It works very well, personally I can vouch for that.

Farrell It works very, very well. So we talk to the patients about this before and the next thing we do is set a date and time for the procedure. These are predominantly performed as outpatient procedures. They do not require hospitalizations. We obviously talk to patients about the risks for the procedure in terms of if they have any cardiac issues, if they have any lung issues, are there any medications that might make the procedure more compromised and we often run into issues whereby more and more individuals are on blood thinners because they have heart stents or other types of hardware and we have an ongoing dialogue with their cardiologist about, should we stop this medication, should we go forward. After all that is done, we then talk about the preparation and typically, the preparation involves the taking of a drink called GOLYTELY or a similar type of liquid that ultimately cleans out the colon and in my mind that actually turns out to probably be the most unpleasant part of the entire procedure, not so much the procedure itself but the preparation involved, but as I said earlier, it is very important that a good preparation and a good clean out of the colon takes place and we actually spend a lot of time with patients talking about the importance of what they take in their diet coming up to the time of the procedure, insisting that they do take the entire preparation. We have them fasting for about six to eight hours prior to the procedure and then they come in on the morning of the procedure fasting. They meet the gastroenterologist. They meet the nurses, the endoscopic technicians as well as the anesthesiologists or CRNAs who may be involved with the procedure, and then the procedure in total takes anywhere from about 30 to 40 minutes or so. The patient is brought into a dedicated private room that has the flexible colonoscope equipment and the patient is asleep for the entire procedure. The procedure is not started until the patient is asleep and then wakes up after the procedure is done.

Hochster I have seen on TV that sometimes people are awake when they are doing this.

Farrell Sometimes people will have an option to be lightly sedated. There are certain places where people will undergo a full colonoscopy without sedation and that is a discussion that we can have with the patient. So one of the discomforts associated with the procedure is we need to inflate or put air into the colon, so that we can really see every crevice, see every turn, see every fold and make sure

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there are no small polyps hiding there. That distention of the colon that goes on with air causes some discomfort and that is the real reason why we offer sedation during the procedure. Now, we can overcome that by removing air intermittently and we have a discussion with the patients and for sure there are certain patients who want to be awake, they want to see what is going on. We are totally okay with that, it is all for the patient's safety, but it does occur from time to time.

Hochster It sounds like a lot of people are involved. We have an endoscopy suite, gastroenterologist, anesthesiologist, that is lot of charges, does insurance cover this?

Farrell Yes, now insurance, both the private as well as Medicare insurance, will cover screening colonoscopy as well as all the follow-up procedures necessary if, for example, a polyp is found or additional testing is done for all the well-defined screening groups that we talk about.

Hochster Since they passed the Affordable Care Act, it is covered by everybody?

Farrell It is still covered.

Hochster But I mean it is specifically covered by all insurance now.

Farrell Yes.

Hochster That is good news for people who are interested.

Farrell It is. I think it has shown its value in terms of mortality and outcome, and I think it would be a very hard thing to try and knock it to reduce coverage because it is such an effective cancer screening tool.

Hochster So the preparation, again, people are drinking liquids for a day or so, they take the GoLYTELY.

Farrell There are a variety of preparations that are available and they are not for everybody and so we have different things available depending on what people wish or do not wish. The typical one involves the taking of a large volume of a drink called GoLYTELY and that is really effective in cleaning out the bowel, but there are other mechanisms whereby we can give smaller volumes of the drink as well and sometimes having the patient change their own diet and going on clear liquids for 48 to 72 hours before the procedure can also be helpful, but the goal is really to have a good clean out and a lot of work goes into the education before the procedure to make sure that when we do the colonoscopy, we will be able to get every aspect of the colon. If that does not happen, unfortunately, we will tell the patient that we did not get to see all the areas that we really wanted to see and that might result in a patient having to come back after a time and that is why we really stress getting the preparation right upfront.

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- Hochster So the preparation is to purge all of the stool from the colon. If you have solid stool in the colon, it is pretty hard to see.
- Farrell If you have solid stool on the morning of the procedure, not only does it make it more difficult to see it, it also puts you at a little bit of risk so we probably do not want to do that procedure on that morning.
- Hochster There is another test that people are interested in, and many people ask about when we talk about this screening is the virtual colonoscopy or what radiologists call CT colonography, so they are really using a CAT scan to take a look at the colon and they have this really cool software that makes it even look like they are going through the colon the same way a colonoscopy would look, I do not know why they want to do that because they are radiologists and are not looking at it, but anyway they do, so what are the pros and cons of that?
- Farrell Obviously one of the major pros of this technology is it is a noninvasive initial approach, so CT colonography is, as you said, the use of a regular CT scan and I have actually undergone some of these myself, you actually lie in a scanner and through the amazing developments that have been made in the world of CT imaging, the radiologist is able to reconstruct what the colon looks like down to small polyps. They are not very small polyps but maybe polyps that are worth finding, so 5 mm, 10 mm polyps or so and as you said, they can recreate what a colonoscopy looks like with flight through simulation as you would do with a video flight game, so the benefit obviously on one side is it is a noninvasive technology, you are lying in a CT scanner.
- Hochster But you still need the same clean out; if you have stool on the wall, it is even harder to find the difference, right?
- Farrell Correct, so there have been some developments that have tried to tag the stool and then remove it using CT radiology but ultimately you do need a good preparation but also one of the other big downsides is that if something is found, you are probably going to need a colonoscopy to find out what it is to do that biopsy, so there are many pros and cons; from our perspective, we are still strong believers in the endoscopic colonoscopy route. What we do realize is that patients are sometimes reluctant or squeamish about it but by them undergoing some form of screening procedure, such as with a CT colonography, it is certainly better than doing nothing and what we have actually noticed is that since the advent of CT colonography, it has been around for about 10 or 15 years now, we end up seeing a lot of patients who get referred because they did not want to have a regular colonoscopy and endoscopic colonoscopy, they chose to have a CT colonoscopy, and some small polyp was found or some abnormality was found that then convinced them that they needed to go on and have the regular colonoscopy, so I think it is kind of a win-win situation for everybody, especially the patients because more and more are getting into the screening scenario.

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- Hochster You also mentioned about, since we know about the DNA changes, about stool testing, so there is some new DNA test out for detecting cancer too. How do you feel about stool testing?
- Farrell Correct and again anything that will get either more patients to pursue colon cancer screening or colon cancer detection, I think are worthwhile, and so anything that is less invasive and does not require sedation and cuts down the cost of this overall, I think is a great advance and so what stool DNA testing has done has really married the technology of stool analysis with a lot of the molecular biology understanding of the development of the polyps and colon cancer and what stool DNA testing is, is it checks and tests for a panel of DNA markers, some of which are clearly indicated and associated with colon cancer development, some that have not been directly associated with colon cancer with a view to try to diagnose cancers and hopefully polyps. I think in this day and age, stool DNA is useful for colon cancer detection. I think for colon cancer prevention, however, there still needs to be more data. And currently, we would still strongly recommend endoscopic colonoscopy over stool DNA testing for that indication.

Dr. James Farrell is Associate Professor of Medicine and Digestive Diseases and Director of the Yale Center for Pancreatic Diseases. 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, archive 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.