

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 a medical oncologist specializing in pain and palliative care and the director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening, in observance of colorectal cancer awareness month, Dr. Miller sits down for a talk with his co-host who is also an internationally known expert in colorectal cancer, Dr. Ed Chu.

Miller I'm going to start by asking you how you got interested in this disease as opposed to other types of cancer.

Chu It was probably a combination of genetics and environment.

Miller Okay, what do you mean by that?

Chu Genetics in that both my parents, as you know, were cancer researchers. They actually got their start here at Yale and then became the founding members of the Brown Cancer Center. Both of them were cancer researchers focusing on trying to develop new therapies for colon cancer. That is part of the genetics story. It also turned out that my mother's baby brother was initially diagnosed with early stage colon cancer in his mid 40s, and then, unfortunately, developed metastatic colon cancer and eventually he died of colon cancer I think when he was 58 or 59. So there is quite a strong family history of colon cancer, which has given me added incentive to try to work in this field. As far as environment, I have just had a number of really exceptional role models focusing on the basic signs of colon cancer as well as on the clinical side trying to develop new clinical therapies to treat patients once they are diagnosed with colon cancer.

Miller Is screening different for people that have a family history than for people that do not have a family history of colon cancer?

Chu The actual screening methods are not different. The age at which one would begin screening is different. For average risk individuals, which probably accounts for 80% to 85% of everyone in the United States, age is the number one risk factor. An age greater than 50 is the recommendation as mandated by the Centers for Disease Control and by the American Cancer Society for undergoing colon cancer screening. There are number of screening methods, which we can get into, but colonoscopy is viewed as the gold standard. If there is a family history of colon cancer, typically the recommendation is to start screening 10 years before the youngest age at which colon cancer was diagnosed. In the case of my uncle, who was diagnosed at the age of 45, the recommendation would be to start screening for me and for his children and my cousins at 35. Perhaps because of my parents' involvement and all of their colleagues and my role models, I got

3:38 into mp3 file [http://www.yalecancercenter.org/podcast/Answers Mar-16-08.mp3](http://www.yalecancercenter.org/podcast/Answers_Mar-16-08.mp3)

my first colonoscopy at the age of 28, and have now had, believe it or not, 4 colonoscopies. For those who are squeamish about the prep and the whole procedure, the fact the matter is that while some of what you hear may be true, a lot of it is myth. The fact of the matter is that screening saves life.

Miller I will ask a question in sort of an odd way; on a scale of 0 to 10, 10 meaning the worst procedural imaginable and zero meaning it was nothing at all, is this a 10 or is it a 0? How hard is it to be screened?

Chu It is not a zero, I would say it is probably a 2 or 3. The very first time I had it done the part that was most difficult was the liquid that you take; it's called GoLYTELY.

Miller Okay!

Chu You have to drink 2 liters of the stuff, and at that time, so 20 years ago, they did not have flavored drinks, you had to drink the entire 2 liter thing, you got bloated, and then 2 hours later you discharged everything; that wasn't so pleasant. Back then, the anesthesia that I was given for the colonoscopy wasn't quite as potent. So back then, I would have said it might have been a 6 or 7 in terms of discomfort level. Both my wife and I actually had almost like his and hers colonoscopies 4 years ago. The drink that you take is now flavored and it is actually not so bad. You go in, they give you the injection and by the time you go in to get a colonoscopy you are out for the count. The next thing you know you are in the recovery room. That is why this has become so easy.

Miller I am over 50 and have had several colonoscopies also. Actually, it is a very easy procedure, and if it is your 50th birthday, let it be your birthday present to yourself, or to a loved one.

Chu Absolutely.

Miller What are the main risk factors for colon cancer?

Chu Just to reemphasize, an age greater than 50 is a very high risk factor. There is no question that diet does play an important role, individuals, and I probably fall into this category, who enjoy red meat, fatty foods, high cholesterol, individuals who do not eat a lot of fiber, fruit, green leafy vegetables, smokers, alcohol and physical inactivity are all the key risk factors. We also know that African-Americans tend to have more aggressive disease. It is interesting, the latest recommendations put forth by the American Gastroenterology Association suggest that African-American should start getting screened at the age of 45, if not earlier.

Miller Thank you for that. A very important point emphasized for Colorectal Cancer Awareness Month.

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Sometimes many people with lung cancer, for example, may develop a cough, or people with skin cancer might see some symptoms, what are the symptoms of colon cancer?

Chu They can vary. Usually the earliest symptoms would be a change in bowel habits, in particular in the size and nature of the stool. Typically if one saw kind of thin pencil-shaped stools, one would be concerned and obviously constipation is a big issue. Abdominal pains, cramps, fatigue, change in the overall energy level and in some cases change in taste or appetite can be symptoms. What should really be emphasized is that in a good number of patients there will be absolutely no symptoms. So the typical response I here from colleagues, friends and relatives is, "I have absolutely no symptoms, why should I undergo that dreadful procedure?" But I would say the vast majority of individuals may not have any symptoms at all.

Miller Nowadays, as compared to when you first started your career, do the majority of your patients have early-stage colon cancer and has that changed?

Chu We are beginning to see more cases of early-stage colon cancer because of campaigns such as Colorectal Cancer Awareness Month and a lot of colon cancer lobbying groups are really pushing to get people to early colon cancer screening and early detection. This is why I think we are seeing patients present at an earlier stage.

Miller Going back to colonoscopy, some procedures that are done for screening are diagnostic and others are therapeutic, how about for colonoscopy?

Chu It is actually a little of both. We know that the precursor for colon cancer is a polyp, and in general it takes somewhere between 8 to 12 years for that polyp to eventually transform and become a true colon cancer. What a colonoscopy does is it looks throughout the entire colon and visualizes the colon. If any polyps are visualized, they are removed. In that setting, you are basically taking away the potential cause for colon cancer; in many ways that is like prevention.

Miller Yes.

Chu Early prevention. Then, if in fact there is a real cancer present anywhere throughout the colon, obviously one can biopsy, make the diagnosis and then hopefully catch it at a much earlier stage. The earlier the stage in which we identify and diagnose colon cancer, the easier it is to cure that individual. With early-stage colon cancer, there is about a 90% chance we can cure that patient.

Miller It sounds like because there is such a long span between when a polyp starts and when it actually becomes a cancer, you've got that window to make a difference.

10:18 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-16-08.mp3

- Chu Absolutely. The one difference in which perhaps the time to go from polyp to colon cancer is shorter than an 8 to 12 year window, is with a familial genetic syndrome called hereditary nonpolyposis colorectal cancer. It was identified by my very good friend, Henry Lynch, who is out in Omaha, Nebraska. Dr. Lynch, along with his wife starting about 40 to 50 years ago, did a phenomenal job tracking and identifying families with colon cancer. In family members who have Lynch syndrome I, the timeframe is 3 or 5 years, so it's accelerated. In that setting, the recommendation is probably to get a colonoscopy on at least a yearly basis.
- Miller Those families you were talking about with Lynch syndrome, a broader question, which is, are there colon cancer clusters with other types of cancers, if there is a family history of other cancers does it raise your worry?
- Chu Absolutely. Dr. Lynch initially identified and termed it Lynch syndrome I, which is only colon cancer, and then he identified and labeled what is called Lynch syndrome II, which is colon cancer also in the context of breast cancer, stomach cancer, uterine cancer, ovarian cancer, pancreatic cancer and brain cancer. There can be a whole range of other tumors, and so that is why I would say to the physicians out there, that when you take a family history, it is not good enough to just see if there is a family history of colon cancer, you want to also know is there is a family history of other cancers. Because obviously if there is, you might then want to send that patient and their family members to a genetic counselor and perhaps to do some blood tests.
- Miller We would like to remind you that you can e-mail your questions to us at canceranswers@yale.edu. We are going to take a short break for medical minute. Please stay tuned to learn more information about colorectal cancer with Dr. Ed Chu, and talk more about March being Colon Cancer Awareness Month.

Medical Minute

Breast cancer is the second most common cancer in women. About 3000 women in Connecticut will be diagnosed with breast cancer this year, but earlier detection, noninvasive treatments and new therapies are providing more options for breast cancer patients and more women are able to live with breast cancer than ever before. Beginning at age 40, every woman should schedule an annual mammogram and you should start even sooner if you have risk factors associated with breast cancer. Screening, early detection, and a healthy lifestyle are the most important factors in defeating breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the one at Yale to provide new treatments, not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at www.yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

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- Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am here with my co-host Dr. Ed Chu. Ed is our guest discussing the latest information on the treatment of colorectal cancer. Ed, we received an e-mail from Barbara who lives in West Hartford. Her question is about using a CAT scan and a virtual colonoscopy for screening and if that is easier.
- Chu Thank you for that great question. As you know, virtual colonoscopy has received a great deal of press recently. It is a very highly sophisticated CT scan imaging of the colon. It can be used for individuals who may not be good candidates for colonoscopy, or patients who have colon cancer with an obstruction and the colonoscopy cannot see beyond that obstruction. To visualize the rest of the colon a virtual colonoscopy can be helpful. The trouble with virtual colonoscopy is that at the end of the day if you see something, the patient still has to undergo colonoscopy. We also know that for very small lesions, virtual colonoscopy will miss that. The reason why people like it is basically because it is over within 15 or 20 minutes and the patient can go back to work without really any ill consequences. But the fact of the matter is that if you are worried about the prep, it is the same prep that one needs to have for colonoscopy, so if the patient can undergo a colonoscopy, that is what they should have.
- Miller If someone is diagnosed with colon cancer and they come here to the Yale Cancer Center, what happens next?
- Chu At the Yale Cancer Center we have a multidisciplinary team of physicians comprised of surgical oncologists who are focused, in particular, on colorectal cancer and colorectal diseases. The team is comprised of medical oncologists like ourselves who focus on chemotherapy, radiation oncologist who obviously focus in on giving radiation therapy, and as part of that team we also have radiologists and pathologists. What will typically happen is that patients will be evaluated by each of the oncology disciplines and then a treatment plan will be designed for that patient.
- Miller I want to ask you about the term adjuvant therapy. How does that apply, what does that mean?
- Chu Adjuvant therapy means that someone had surgery and there is an indication for giving what is called followup chemotherapy, so adjuvant, after the fact. Currently for colon cancer, in patients with so called stage III disease, meaning the cancer has spread to the local regional lymph nodes, there is a clear indication for giving chemotherapy. The standard of care right now is what is called Folfox chemotherapy. For those who are not good candidates for that more aggressive therapy, either a drug called 5-FU or an oral pill called Xeloda is appropriate. In patients with stage II disease, where the colon cancer is confined to the colon and has not yet spread to the local regional lymph nodes, that is an area of controversy. In my own view for individuals who have so called high-risk stage II disease, I offer and recommend chemotherapy, either the more aggressive Folfox, or 5-FU or oral Xeloda. Where things are now changing a little is in the average or low

17:30 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-16-08.mp3

risk stage II disease. There it requires a very careful and thoughtful discussion between the physician and the patient discussing the pros and cons of whether or not the chemotherapy will really be a benefit and then also weighing in the potential risks and side effects of the chemotherapy treatment.

Miller These are tough decisions for people to make. How do you find that people eventually make the decision? I mean do they get ten opinions and come down to a gut feeling?

Chu These days' patients and their family members are so well educated and sometimes for these very difficult decisions they may go and try to get two or three opinions. It is interesting, there are two online websites for adjuvant therapy of colon cancer. One is adjuvantonline.com and the other one is on the Mayo Clinic website. They have algorithms and can actually pinpoint the real benefit of getting adjuvant chemotherapy, but at the end of the day a large part of it depends upon what the physician recommends and their gut instinct.

Miller For patients who have advanced colon cancers, what are some of the things you are really excited that are arriving at the forefront?

Chu One of the tremendous advances that we have seen just within the last 6 to 8 years is the development of new chemotherapy agents and the development of new target therapies to treat patients who have what is called advanced metastatic colorectal cancer. There has also been a great effort to try to develop new therapies that can maintain the activity of these new therapies, but also maintain and support quality of life. One very interesting study that we're about to embark on is a study that combines a chemotherapy drug called irinotecan, which has been around now for about 12 years, and a Chinese herbal medicine called PHY906. This is the next inline and we are going to be looking at the ability of this herb to impact the side effects of irinotecan. In earlier studies we had found that this herb could reduce nausea, vomiting and diarrhea associated with chemotherapy and so we are hoping to see the same things, but now we are also looking to see whether or not this herb may be able to enhance the clinical activity of irinotecan. We are also doing a number of very interesting scientific studies to try and see if what happens in the patients, happened in the animal studies that have been done here at the Yale Cancer Center.

Miller Can you talk about this bench to bedside and then back to bench process?

Chu That is one of the real strengths that we have at the Yale Cancer Center, to take the phenomenal science that is going on in the laboratories and bring them into the clinic, and then based on the clinical studies and the clinical observations, take things back into the lab. It is kind of an iterative process. This herb PHY906 was identified by my close colleague, Professor Tommy Chang in pharmacology, who is kind of my partner in crime in a lot of things that we do in our drug

21:24 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-16-08.mp3

development program at the Yale Cancer Center. He went back into the literature, which covers about 3000 years, to look for an herb that was used in everyday practice to treat nausea, vomiting, abdominal cramps and diarrhea, and he found this herb. Of course it was not called PHY906, it was given a Chinese name, and I apologize to my parents who may be listening tonight that I cannot pronounce it, but there is a Chinese name. This herb has been used in the Orient for well over 2000 years and Tommy and his laboratory group found that in fact it significantly reduced the toxicities of a number of chemotherapy drugs and seemed to stimulate the immune system within animals and was able to enhance the antitumor activity of a number of drugs. Based on those very interesting scientific discoveries, we decided to then bring that into the clinic.

Miller There is another drug that I am reading about and is being tested at Yale, IMC-A12.

Chu Yes, that is a very interesting molecule that is being developed by InClone pharmaceuticals. This is an antibody that inhibits the insulin growth factor receptor I signaling pathway. Now that is a pretty fancy term, but what we are finding is that in colon cancer, as well as in a whole host of other tumors, there are a number of critical signaling pathways that are turned on that allow the tumor to continue to grow. There is another antibody that the folks at InClone have developed, it is FDA approved for the treatment of colon cancer called Herbatox, and that inhibits the epidermal growth factor receptor signaling pathway. Those two pathways are parallel to one another and what the scientists here at Yale, and at other places, found was that if you treat with an antibody that targets the EGFR pathway, it actually stimulates this insulin growth factor pathway. The idea was that if you then had antibodies to both, that might do a better job. We did the first phase of the study and are about to start the second phase of the study; it is a very-very interesting molecule. In addition to InClone, there are a number of other companies that have developed similar antibodies which we are also hoping to test here at Yale.

Miller This is almost like a second generation of targeted therapies, therapies that go after something specific. When you combine agents like this that are attacking the cancer in different ways, do you get double or triple the side effects?

Chu No, it is really quite remarkable about these antibody therapies. These targeted antibody therapies do not seem to cause worse side effects or worse toxicities, either when you combine them with chemotherapy or when you combine them with other antibodies. It is interesting to note that Lyndsay Harris, who heads our Breast Cancer Program, has found that in women with breast cancer who have been treated with the antibody Herceptin, that same insulin growth factor receptor pathway is also activated. We are actually thinking about trying to combine Herceptin with this and/or other antibodies that target this pathway to see if it might actually create greater effects in women with breast cancer.

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- Miller Any predictions? You have been involved in colon cancer for many years here and have been at the forefront in terms of research. What do things look like 5 years from now, 20 years from now for patients with colon cancer?
- Chu The focus right now is to try to develop molecular markers that can help to identify which patients will or will not respond to particular therapies, either chemotherapy or the targeted therapy and/or to identify which patients may experience increased toxicity. We are still at the beginning stages of this, but I think that all of those that are focused on colon cancer are hoping that over the next 5 to 10 years we are going to move away from so called empiric therapy and really get individualized and personalized medicine. We are beginning to see this with lung cancer, and breast cancer has been the poster child for a number of years. We are beginning to see some examples for colon cancer, but as the molecular revolution continues to go forward at an incredible pace, we will see more of this.
- Miller There are a lot of drug studies and a lot of things to learn. In the United States, what is the participation rate for patients being involved in clinical trials?
- Chu Unfortunately it is still quite low, and if you look at the national statistics put forth by the National Cancer Institute, it is less than 5% of all patients' with cancer that go onto clinical trials. Obviously at NCI designated cancer centers we do a little bit better. At the Yale Cancer Center we are probably closer to 10% or 11%, but what we are striving to do is hit 15% to 20%.
- Miller As this show comes to close, Ed remind us of good screening for colon cancer.
- Chu The key message is that screening and early detection saves lives. The gold standard for screening is colonoscopy and if you are age 50 or greater, with no family history, and have not had your colonoscopy, please go out and get screened.
- Miller Great message Ed, I want to thank you for being our guest on the show.
- Chu Thanks Ken, it is always great being with you.
- Miller I want to encourage all our listeners to please talk to your family and yourself about having the proper colorectal cancer screening. On behalf of myself and Yale Cancer Center Answers, we want to wish you a safe and healthy week.

If you have questions, comments, or would like to subscribe to our Podcast, go to yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week you will meet Dr. Lyndsay Harris and Gina Chung who will join us to talk about the latest treatment options for breast cancer.

