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Welcome to Yale Cancer Answers with your host doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about colorectal cancer with Doctor Michael Cecchini. Doctor Cecchini is an assistant professor of medicine and medical oncology at the Yale School of Medicine where Doctor Chagpar is a professor of surgical oncology.

So Mike, maybe we can start off by you telling us a little bit about colorectal cancer. The epidemiology. Who gets it? How common is it? How lethal is it?

And then we’ll get into some of the more recent updates with regards to screening of colorectal cancer. I am a gastrointestinal medical oncologist, and I see a variety of GI cancers, colorectal cancers and it is where
I focus the majority of my research. It’s quite common. There are about 150,000 cases diagnosed annually in the United States and more than 50,000 annual deaths. And I do think it needs to be stated that there is also a rise in incidence in adults less than age of 50. Although it is like many cancers, predominantly a cancer of older individuals, for some unclear reason, the incidence is actually rising in adults less than age of 50, while it is going down overall, due to effective screening by colonoscopy for adults over the age of 50.

Patients with a personal history or family history of colorectal cancer are at increased risk for developing the disease. Personal history for large polyps etc., certain polyps with certain characteristics increase the risk for colorectal cancer, but it is mostly sporadic, not familial. There are conditions like inflammatory bowel disease, prior radiation and then in rare circumstances inherited syndromes such as Lynch syndrome and something called FAP. Familial adenomatous polyposis syndrome.
And other polyp syndromes. So when thinking about the fact that the majority of these are sporadic, are there any risk factors that people who don’t have a family history should really be cognizant of? So I’m thinking here about things like you know, people often ask about smoking or alcohol, or smoked meats or other things that might increase their risk. There isn’t this clear association with some carcinogen, some cancer predisposing factor, like there is with lung cancer and smoking. I’d say that the data is a bit mixed on how important certain risk factors are. Certainly things like obesity, diabetes and red or processed meats increase risk and they may affect the rate to some degree, but the data again isn’t always consistent. The smoked meats issue is more thought to be related to gastric cancer or certainly seems to play a bit more of a role. Race also plays a role.
African Americans have the highest colorectal cancer rates in the United States and mortality is also higher compared to other ethnic groups. So do we know why we see some of these epidemiologic trends? Why is it that more African Americans get colorectal cancer? Why is it that we’re now seeing more colorectal cancer occurring in adults younger than the age of 50? What are the factors in these particular populations that’s increasing their risk? The short answer would be we don’t know, and where there’s a tremendous effort in trying to understand some of the risk factor and some of the reasons for the increased risk in the groups that you just articulated. Interesting and to get back to the younger age group, it’s not just that the incidence has been static in that group, it’s increasing and so we do think that it has some lifestyle factors, perhaps diet is a factor that is playing a role here, but we really don’t know,
and there’s a tremendous area of research to try and understand why these incidences are increasing in the young adults.

But we don’t know.

And so as we see more incidence in younger people, one of the questions that might come up is, you know historically, and I know that the screening guidelines have recently changed to include younger people in terms of routine screening for asymptomatic people. But when we think about the fact that over the last several years, we’re starting to see more colon cancer in younger people, how is it that they present because presumably because historically the guidelines had recommended starting colorectal screening at the age of 50. So how are we picking up these cancers in younger people?

Unfortunately, it’s the last thing on many caregivers minds, medical professionals minds that somebody symptoms would be related to colon cancer if they are a younger adult. But the majority of patients, about 3/4 of patients, will have some
nonspecific change in their bowel habits.
Half will have bleeding.
There’s a palpable rectal mass in about 1/4 of patients,
and iron deficiency, or anemia isn’t actually a sensitive as you might think.
It’s fewer than 20% of patients,
especially young adults that would present with iron deficiency anemia.
So unfortunately, I have numerous patients in my practice that had some lower GI bleeding that was attributed to hemorrhoids and incidence wise.
Individuals should also listen to their bodies, and if something’s not right, change in bowel habits, bleeding, should take those very seriously, even if they’re younger.
Is it the case that we’ve seen this increasing incidence in younger people because they are presenting with symptoms?
Presumably because screening was not recommended for people who were younger than age 50?
Is it the case that these younger people that we were
seeing colorectal cancers in were actually presenting with a higher stage, and what implications does that have for prognosis?

Yeah, that’s completely correct. Unfortunately, when you have a disease that is presenting because symptoms develop instead of asymptomatic screening, generally this stage is higher, so these younger adults generally are diagnosed at a more advanced stage and sometimes have even more aggressive biology overall. So again, the stage is going to be higher. The younger adult population tends to do better than the older adult population for when you’re matching them by stage, because they can probably withstand treatment better but they are diagnosed at a more advanced stage then the patients that are diagnosed by asymptomatic screening and so now the American Cancer Society has come out and said that they recommend starting screening at the age of 45. Can you tell us more about their recommendations?

Absolutely. The American College of Gastroenterology initially recommended
dropping the screening age to 45 for adults at average risk, but the most widely followed guidelines are actually the US preventative Task Force guidelines, which the majority of primary care physicians follow, and they did change their recommendation about a year or two ago to propose a Grade B recommendation for adults over the age of 45. But they still kept the greater recommendation for adults over the age of 50. But just yesterday this was updated and now for all adults, they’ve listed a strong recommendation for adults over the age of 45, so I think now going forward that’s really going to be the age we start screening almost all asymptomatic adults. Colonoscopy is a very powerful screening procedure, not only because they can diagnose a cancer that’s there and then we can deal with surgery or chemo as necessary, but they also remove premalignant conditions. So they are helping prevent the development of colorectal cancer even down the road.
so many screening tests now are recommended or that at least individuals could consider. So colonoscopy is often thought of as the gold standard, but some of these other tests seem to be really quite easy. Tell us a little bit about the different tests and the advantages and disadvantages of each. What do you recommend for patients who come to you and say, I heard about the updated guidelines, I’m now 45. What test should I have? It’s not exactly my area. The majority of patients I see have already been diagnosed with cancer, but absolutely colonoscopy is still the gold standard, so that would be my kind of blanket recommendation. For those that aren’t ready to do that, but are interested in doing some screening, there are test for fecal occult blood, so for small amounts of undetectable blood and that’s an imperfect way to assess whether or not there’s a cancerous or precancerous condition.
Again, the colonoscopy offers the power to remove precancerous lesions, which probably are not doing much at that point in time, but maybe missed by a test we’re trying to detect small amounts of blood in the stool. There are also tests that actually try to detect DNA in the stool, and that may be a more sensitive way, but also we’re not removing anything premalignant with that we have yet to develop a blood based test that’s diagnosing cancer before it develops, or at an early stage. So there are companies that are working on that, but we have a ways to go, but most of these patients are seen by my colleagues in Gastroenterology for their screening discussions and they are able to give some more eloquent answers than I am.

Mike, the other question, and this might be a tough question as well, is why the magic number of 45? I mean, if we’re seeing patients with younger colon cancers, why is it 45? Why not 40 or 42 or 38?
These numbers as to at what age people should start screening? That’s a great question and somebody asked the same question just last night. And I feel the same sentiment as well. I think that this is a first step and we may be recommending 40 in a few years, but we’ll have to see how the data and the number needed to treat the number of colonoscopies done to really prevent one colorectal cancer holds up over time at these younger age groups. There’s also the number of mammography as well. But again, getting back to the time it takes for colorectal cancer to develop in general somewhere on the order of a decade, I think by lowering the age to 40 we’re really capturing that group. If we were to lower the age of 40 we’re really capturing that group in the 45 to 50 range versus right now with this age of 45. Or probably we’re helping prevent higher incidence in that 50 to 45 range. But as we started out the discussion
really less than 50 is still seeing an increased incidence of colon cancer. So I think this is a moving target and we will benefit over time lowering the age, and I certainly, unfortunately, see patients in my practice below the age of 40 and 30 sometimes. Certainly it’s going to be a moving target that we will follow, but for right now we’re going to take a short break for a medical minute. Please stay tuned to learn more about the treatment of colorectal cancer with my guest doctor Michael Cecchini. Support for Yale Cancer Answers comes from Astrazeneca, working to eliminate cancer as a cause of death. Learn more at astrazeneca-u.com. This is a medical minute about lung cancer. More than 85% of lung cancer diagnosis are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer for lung cancer patients. Clinical trials are currently underway to test innovative new treatments. Advances are being made by utilizing targeted therapies and immunotherapy.
The battle two trial aims to learn if a drug or combination of drugs based on personal biomarkers can help to control non small cell lung cancer. More information is available at yalecancercenter.org.

You're listening to Connecticut public radio. Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I'm joined tonight by my guest doctor Michael Cecchini. We're talking about the treatment of colorectal cancer and Mike right before the break we were talking about the new updated screening guidelines, which now are recommending screening for colorectal cancer going back to the age of 45. One last question with regards to screening, before the break, you had mentioned that there are certain racial groups, for example, African Americans that tend to be diagnosed at a higher frequency, tend to have a worse prognosis than their Caucasian counterparts. So are the screening guidelines any different for African Americans versus Caucasian patients?
There are slightly different recommendations just as of yesterday the US preventive taskforce has changed it 45 and above for all adults and so I think there were some high risk groups including African Americans that were recommended 45 and above previously. But now it’s just everybody 45. One wonders whether they will, as we were talking about before the break and edging even earlier, whether they would make that now a new age for higher risk groups. But I want to switch gears now and talk a little bit about what happens to patients after they have been diagnosed with colorectal cancer. So somebody goes and they get their colonoscopy and you know, their colonoscopy and you know, they talked about colonoscopy being a great modality that can actually find premalignant lesions and remove them. But let’s suppose on colonoscopy a patient is found to actually have an invasive cancer. Tell us a little bit more about how the treatment really works in terms of managing patients with colorectal cancer. Absolutely so it’s a very
multidisciplinary effort, meaning there's numerous care providers that are involved in navigating somebody through a diagnosis of colorectal cancer.

There's myself as a medical oncologist, there are our surgical colleagues. There's our pathologists, radiologists, our radiation oncologists. Our nutritionists, social workers, everybody really involved here, so the first step to really know how we're going to treat somebody's cancer is the stage. So that's not unique to colorectal cancer, it is very common in cancer. The stage will help dictate what the care is going to be. Stage 1, 2, 3 and four is how we stage the cancer and I could probably spend hours talking about all of this. But stage one is basically a small cancer that's barely invaded the cancer and I could probably spend hours talking about all of this. But stage one is basically a small cancer that's barely invaded into the wall of the colon. If we think of the colon as a tube, it's barely in.

It starts on the inner part of that tube. It's barely invaded through the wall, and a tumor like that is just excised by surgery. They may never even see me as a medical oncologist because surgery
is curative in the majority of cases.

A stage two cancer has gone a little bit further into that wall, but hasn’t spread to any lymph nodes. Those patients will see a medical oncologist and it will be discussed whether or not they get chemotherapy after surgery to increase their cure rate and eradicate small amounts of possible residual disease based on risk factors.

Stage three cancer means it’s gone to the lymph nodes, so it’s behaving a bit more aggressively so a patient with an invasive mass, a colonoscopy is done. A surgery is done, lymph nodes are removed at the time of surgery in addition to the tumor if there’s cancer in the lymph nodes.

So if it’s a stage three cancer, all of those patients are going to see a medical oncologist. And almost universally, as long as they’re healthy afterwards, will get chemotherapy to hopefully increase their care.

Like with many other cancers, stage 4 means it’s spread more distantly, so cancer that started in the colon
spread to the liver, the lung, the lining of the abdomen, which we call the peritoneum, would make a cancer stage four. One of those spots would make a cancer stage four, and there still may be a role for surgery. But chemotherapy is generally. Generally, where we will start, we think of it as a systemic disease throughout the body, and chemotherapy works throughout the body. When it’s working in those stage four cancers, though, there’s a lot that we need to know to personalize the therapy for the cancers. We do a lot of tests in the lab and to characterize the cancer, is it mismatch, repair, deficient or not? Are there mutations in genes called RAFS or not? And they tell us how we tweak the chemo, or maybe even offer immunotherapy to the patients, and then again, we will sometimes consider surgery to remove distant metastases in select cases, and that’s why it’s so important to have a multi disciplinary team. So a true team involved in the care of these patients, even with stage four disease and all
of these cases are reviewed at our tumor board with that whole team, I articulate how best to approach somebody's care in terms of these molecular genetics. The RAF mutations, the mismatch repair mutations you mentioned those in terms of tweaking chemotherapy for stage four, are those also used in kind of tailoring therapy for people with earlier stage disease? If I could only know a couple things about the molecular characteristics of somebody's tumor, it would be the mismatch repair status, which is also sometimes called the microsatellite status or their RAF status. So in localized disease, the mismatch repair status is very important. The RAF and the RAF status is not so important, so we often only send the latter component for metastatic disease. But for localized cancer mismatch repair, deficient, or microsatellite instability high cancers generally have a more favorable prognosis, and sometimes we will take that information and say you don't even
need chemotherapy after surgery because of this finding of mismatch repair deficiency or microsatellite instability and it’s less likely to come back and therefore you don’t need chemotherapy. There’s a lot of other factors that come into play there, so I don’t want to say that all mismatch repair division microsatellite instability high tumors don’t need chemotherapy after surgery, but it’s generally thought to be a good prognosis. And we know from metastatic disease, those tumors are much more sensitive to immunotherapy. Some of the most sensitive cancers that there are in fact to immunotherapy, and it’s being investigated whether or not immunotherapy is going to increase cure rates in that population. And we have some of those clinical trials going on. That brings me to the next question, which is about clinical trials. Colorectal cancer has been around for a long time and is one of the leading cancers affecting both men and women, and so presumably there are some.
pretty standard regimens in terms of chemotherapy that we offer these patients.
So tell us a little bit about when you offer people a standard regimen, and when you offer them a clinical trial?
Clinical trials play a tremendous role in the management of a disease like colorectal cancer. And are really how we move the field forward and we’ve doubled and tripled the survival rate especially for metastatic disease over the last few decades. And that’s because clinical trials brought new agents and drugs and treatment approaches into the fold and the treatments we have for metastatic disease, we use some of them again after surgery we use drugs, and we like our acronyms or abbreviations so we have a regimen we call folfox which is 5FU, and oxaliplatin and a vitamin called leucovorin. It’s really two chemo drugs together and we have another chemo regimen called FOLFIRI. so again two chemo drugs together just a second one instead of the oxaliplatin, and that’s really the backbone of our care, and we can usually control a metastatic colorectal cancer patient for years with those two regimens together,
but at some point we run out of mileage with those agents, resistance develops, tolerability becomes an issue, something that necessitates us moving on from those regimens. And we really don’t have great agents after that, so I’m often thinking about clinical trials, novel clinical trials after those regimens have stopped working, but I am often thinking about clinical trials even initially where those agents will be added on, agents will be added onto those chemo drugs, so they are good chemo backbones. We can do better and we are investigating numerous ways, adding an immunotherapy, new targeted drugs, new chemo drugs to those regimens. But we’re also investigating completely new regimens in the 3rd and the 4th line setting. There are third and fourth line drugs available for patients with colorectal cancer, and there’s a drug called task 102. But the effect of those is marginal compared to those other therapies that I mentioned.
It sounds like clinical trials have two kinds of roles. One is after our standard tried and true regimen have failed and we’re looking for the best thing that might help and move us further afield. And the other is in investigating novel therapies and straight out of the box.

These treatments like folfox and folfiri have doubled and tripled the survival rate. But we can still do better than that. But they are the standard of care, and since they are so effective, we add on to those and we should add on to those so that patients get the best treatment available to them. When we’ve moved on to our third and our first fourth line, treatments is task one or two and start chemo pills. There is not a great alternative. They are not tolerated super well and their time with Disease Control is not so good as we would like, so that is a time that we try a more novel approach generally.
your research and some of the things that you’re particularly excited about in this field.

I guess maybe I’ll start by talking about some of the things I’m excited about more broadly, and one area that I think has garnered a lot of attention lately for colorectal cancer is something called circulating tumor DNA, where we can detect minimal amounts of circulating tumor DNA in the bloodstream after a surgery. So, for example, patients with stage two colorectal cancer that happens to have a blood test done that circulating tumor DNA is detected. Now we know that that patient is probably going to relapse if we don’t do anything besides observation, so we can use a tool like that to decide who’s high risk, who’s low risk and that gives us opportunities to intensify and deintensify treatment. So trying to increase cure rates for those that are high risk but also knowing when somebody is going to do well and maybe avoid circumstances of over treatment. So that’s something as a field I think we’re learning.
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colorectal cancer Group, for example.

This is a trial where we’ve come up with the idea, and maybe we’ve written a grant or we’ve partnered with a drug company to tell them in a way that we think that we could look at a new subtype of cancer, or a new way to look at their drug to leverage that and for patients with that disease,

so I have an investigator initiated trial for colorectal cancer that is received two different types of chemotherapy, where we look for a marker called MGMT. So we basically meet a patient, if they are potential candidate we will test their tumor for this marker, and if they have this marker which ends up being about 40% of patients if they have this marker, we will then offer them enrollment in a clinical trial. So we basically identify this subgroup of colorectal cancer and then we had this trial that we came up with here at Yale. And we’re also studying the outcome of patients with this to make sure that we’re actually helping people, but also studying the science to develop the next generation of trials which, in my opinion will be leveraging the immune
system to make it work for the majority of patients with colorectal cancer as my colleagues in lung cancer and Melanoma have been doing for the last decade.

Doctor Michael Cecchini is an assistant professor of medicine and medical oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at yalecancercenter.org.

We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public Radio.