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 could 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 continue 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 Cancers Program at Yale School of Medicine. Dr. Hochster will be speaking with Dr. Xavier Llor. Dr. Llor is Medical Director of the Colorectal Cancer Prevention Program and Co-Director of the Cancer Genetics and Prevention Program at Yale School of Medicine. Here is Dr. Howard Hochster.

Hochster Could you tell us a little bit about yourself and how you got involved in colorectal cancer and genetics of colorectal cancer?

Llor I started when I landed at a lab at the University of Chicago that was studying molecular mechanisms of colon cancer development and that started my interest and I continued my interest through my fellowship and then onto my academic career. At the same time that I was working on research, I started developing my interest in clinical cancer genetics and basically taking care of families who have inherited colon cancer syndrome, so both my research and my clinical interest kind of merged into this field of colon cancer.

Hochster You are a gastroenterologist?

Llor Correct.

Hochster So you did internal medicine training and all the training that other gastroenterologists have done as well as research on genetics?

Llor Yes, correct.

Hochster And did you do additional training in the area of genetics as well?

Llor I actually have a PhD in Molecular Medicine and it was also based on colon cancer genetics.

Hochster Tell us a little bit about the genetics of colon cancer and what leads to colon cancer?

Llor It is a multi-stage process where there are several genes that develop mutations. When these mutations start falling in areas that are keen to the control of development and growth of the human cells, these end up developing into a cancer. It is a long process. We think that colon cancer takes several years to develop, even up to 10 years and is the result of these different

3:15 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

molecular alterations, genetic alterations that end up developing into a cancer. This is a very well described process but we keep adding more and more information as we learn more not only about the genetics, but also about what is being called the epigenetics, the modifications of the genetic information afterwards.

Hochster We know that DNA in the colon lining cells, what we call the epithelium of the colon, has kind of a predictable pattern of events of mutations that lead up to the development of colon cancer.

Llor Correct, and there are several pathways of molecular alterations that end up developing into colorectal cancer and these are different phenotypes or ways of cancer developing, but many of them are actually shared by the different molecular alterations we are talking about.

Hochster And has that lead to any improvements in the treatment of colon cancer or prevention of colon cancer?

Llor Certainly, for instance, some of these markers are used in the stool based test for early detection of colon cancer, and some of those markers, as you will know as an oncologist much better than myself, some of these mutations, KRAS mutations, for instance, are being used as part of the armamentarium in terms of deciding about chemotherapeutic agents, so actually they do have a role both in diagnostics and also in therapeutic decisions.

Hochster You mentioned stool testing, and the FDA this year approved a test based on collecting stool and looking at the DNA for some of these known mutations and then there are other ways to test the stool for blood and so forth, how useful are those kind of tests?

Llor I think there has been a lot of research done and quite a bit of progress. We may not be there yet in terms of those being the methods of choice for colon cancer screening, but the test you mentioned, the stool based test, is already a slight improvement in comparison to the ones that are based on fecal occult blood but more improvements need to be made for it to really be a very solid alternative. When it comes to blood based studies, there are actually several studies being performed and some companies with tests out there are mostly based on methylation or at least what we are talking about these epigenetic changes in the genome that they base their tests on and again, those do need even more studies in order for us to better understand how good of an alternative they are for colon cancer screening.

Hochster Previously, people used to take a little bit of stool, put it on a card, give it back to their doctor to test for blood in the stool using a chemistry test, and now you can send your stool, you have to pack it up, and you can send it to a laboratory that will actually look for some of these DNA mutations in the stool and therefore tell you, you have to go for a colonoscopy, I guess?

7:04 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

Llor Exactly, again the ultimate diagnostic tool is colonoscopy and not only the ultimate diagnostic tool but also the most preventive tool because through removal of polyps, that is how we prevent colorectal cancer.

Hochster That is kind of a key concept, I would like to reemphasize for our listeners this evening, colonoscopy can actually prevent colon cancer if they find these polyps, these adenomas before it becomes cancer and it is removed at the time of colonoscopy, you will not get cancer.

Llor Exactly, that is something that only through colonoscopy we can do and we believe that the slow but steady decrease in colon cancer incidence in this country is mostly due to this widespread use of colonoscopy and removal of these polyps.

Hochster We are already seeing in the United States today that the incidence of colon cancer has gone down about 10 to 20,000 cases a year and that seems to be the effect of people going for screening colonoscopy and therefore, they never get colon cancer which is obviously quite a good outcome.

Llor It is interesting also that colon cancer incidence started going down in the 80s when colonoscopy was not as widespread as it is now, so we believe that there is also some changes in the environment in our country that probably is pointing towards the incidence going down but I think from where we gathered all the numbers that we can get, a decisive difference has been through the widespread use of colonoscope.

Hochster So, is that due to dietary changes, what influences us getting colon cancer to begin with?

Llor Probably the strongest factors in colorectal cancer development are more environmental and dietary than anything else and there have been studies associating tobacco and alcohol consumption, a high BMI or high body weight, lack of physical exercise and some particular dietary habits that have been consistently associated with colon cancer development. What is less clear is how much of changing these habits can prevent colon cancer, but study after study has shown that actually these factors do play a very important role and that would also be backed by the studies of migraine populations from low incidence countries to higher incidence countries like ours where rapidly in one generation the population adopts the frequency of colon cancer than the local population, so certainly that points towards the environment playing a very important role.

Hochster Is it what we eat or just the fact that people are heavier and fatter?

Llor Maybe it is everything. There is a very well conducted study from a large cohort in Europe called EPIC that they put together all these different factors and actually in a way it seemed to add up a little bit, so the more factors that we mentioned before that you have, the higher the chances you have to develop

colorectal cancer, so while this is not the math, it looks like probably there are some additive defects of this different deleterious factors towards cancer development.

10:40 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

Hochster For a while the National Cancer Institute was telling everybody to eat fiber and have a bran muffin for breakfast, and that does not seem to be around so much anymore.

Llor Actually, when you look at the main initiatives of the American Cancer Society, lifestyle modification and all these factors seem to be playing a very important role or initiatives such as bringing fresh food to desert areas where people do not have access to fresh food, that seems to be highly backed by the American Cancer Society, recognizing the important effects of these environmental and nutritional factors that are particularly worse in the less favored populations in our country.

Hochster And exercise seems to be important too. I know that Dr. Melinda Irwin here in our School of Epidemiology is actually conducting some randomized trials involving exercise for colon cancer prevention.

Llor It makes a lot of sense because many of the epidemiological studies have shown that there is a clear association, so it makes sense to do this intervention and see how we can prevent colon cancer. Hochster So lifestyle modification can include dietary, exercise and things like that that may actually help us bring down the incidence of colorectal cancer, but colonoscopy seems to be the key thing that can actually prevent people from progressing to getting colon cancer, we can catch the disease at a time before it becomes malignant, and can you tell us a little bit about colonoscopy?

Llor Basically colonoscopy is a test that is done using a flexible rubber tube that is the size of a little finger that we put through the anus and we look at the entire colon or large bowel and basically, what we do is we thoroughly look for the presence of these polyps which are little growths in the mucosa and those are the ones that can eventually develop into cancer if they are left alone, so through colonoscopy, we can remove a great deal of them and it is through the removal of these polyps that the risk of colon cancer does go down dramatically.

Hochster So the gastroenterologist takes a scope, takes a look around the whole colon and if he finds a polyp, takes it out, and that is diagnostic and preventative?

Llor Exactly, but we do know that not all polyps would develop into cancer, we do not have a way to know which ones would develop into cancer and which ones would not, therefore, we remove them all and removing them all, we have good data showing that yes, we decrease drastically the incidence of colon cancer, so there is no question that some of those that we are removing would end up being cancer if left alone in that colon.

Hochster Would the patient feel it if they were taking out these polyps?

13:49 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

Llor The colon is an interesting organ. You do feel it when we are stretching it, which is how the colon communicates to us that we need to go to the bathroom. Yet, when we make a little cut, our colon does not feel a thing. It is not primed to feel these kind of feelings. On top of that, we are doing a colonoscopy through either deep sedation or anesthesia; therefore, it is even less painful, but again, just removing a polyp in itself, because of the anatomy and how we are wired, we do not feel it.

Hochster Thank you Dr. Llor. We are going to take a short break for a medical minute and then we are going to come back to learn more about colonoscopy and risk factors for the development of colon cancer. You are listening to Yale Cancer Center Answers and I am here tonight with Dr. Xavier Llor.

Medical Minute Breast cancer is the most common cancer in women. In Connecticut alone, approximately 3000 women will be diagnosed with breast cancer this year and nearly 200,000 nationwide, but thanks to earlier detection, non-invasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40, or earlier if they have risk factors associated with breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to make innovative new treatments available to patients. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. This has been a medical minute brought to you as a public service by Yale Cancer Center Cancer 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.

Hochster Welcome back to Yale Cancer Center Answers. This is Dr. Howard Hochster and I am joined tonight by my guest, Dr. Xavier Llor. We are discussing colorectal cancer. Xavier, you were telling us about what is involved with colonoscopy and we said that you could do the biopsies and you would not feel it and it is really more that you blow air in there that is uncomfortable, so what does the patient need to do to obtain a colonoscopy and who should be getting colonoscopy for screening?

Llor Basically everyone who has an average risk, meaning no family members with colon cancer should be getting colonoscopy starting at age 50; if you are African American, age 45. There is enough evidence showing that African Americans do develop colon cancer earlier, and that is why we want to screen them sooner than the rest of the population.

Hochster Let me just repeat that. Everybody, no matter if somebody in your family had colon cancer or never had colon cancer, no risks, once you turn 50 if you are Caucasian, you should go for

17:07 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

screening colonoscopy and if you are African American, you should start at age 45, those are for people who have no other specific risk factors.

Llor Exactly. If there is family history or other factors, those should be evaluated in a more specific way. We are talking about people who do not have any special risk factors as we were saying before.

Hochster And we know from studies that have been done, large randomized studies, with 10 years of follow- up, that actually removing polyps prevents people from getting colon cancer, so colon cancer is largely a preventable disease today. We just need to get people to go for the test that nobody really wants to think about and they certainly do not want to consider the preparations for it, nobody likes to think about their colon, so it is a little bit of a challenge for us. What do people need to do about preparing for colonoscopy? Is that something they should worry about?

Llor Probably that is the toughest part, "toughest" because it is very important that when we do the colonoscopy, the colon is perfectly clean. If it is not clean, we can miss little polyps, so patients have to take a preparation, half of it the day before, half of it usually on the same day of the procedure, and they take several glasses every 10 minutes, but basically, the whole idea is really cleaning up the colon really well, so we make sure that when we do the colonoscopy, we are not going to miss any little polyp, and we can see everything.

Hochster If you are mostly clean, you can wash it off, some stool on the wall, is not so bad, but you really need to get everything out more or less because if there are still solid stool, you are not going to be able to see.

Llor Yes, exactly, at least everything liquid. If it is solid, it is a problem and it is very uncomfortable to feel that we have not been able to see the colon well enough and we may have missed a lesion or a polyp and that is what we do not want to face. Hochster Then after the clean out, they come, usually to the outpatient unit, where you have a colonoscopy suite, the next morning after they prepare and then it is done with sedation or anesthesia.

Llor Exactly, sedation or anesthesia, in general it is a very easy procedure. Most patients tell us that the hardest part was the preparation and not the procedure itself.

Hochster And that is who should get a colonoscopy if you are average risk. Who are the people who have higher risks of colon cancer today?

Llor About 15 to 20% of individuals do have at least one first degree relative with colon cancer, and that puts you in a different category to start with. If

the lifetime risk of developing colon cancer in the US is about 5%, having a first degree relative puts you in a 10-15% lifetime risk, so it increases

20:15 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

your risk significantly and that is why in general, we recommend you start sooner with colonoscopies and actually do them more often, every 5 years instead of 10 years if there are no polyps. If there are polyps, then that can vary.

Hochster So if you have a first degree relative, in other words a parent or a brother or sister who had colon cancer, you are at a higher risk and you should go for colonoscopy? When is your first screening colonoscopy supposed to be done?

Llor It is usually at age 45 or if the family members are relatively younger, it will be 10 years before that cancer was diagnosed, 10 years earlier than the age that the cancer was diagnosed in the family member, so that is why we have to really customize that screening to the particular circumstances of that family.

Hochster Again, if your parent or your brother or sister had colon cancer, you should go for screening colonoscopy starting at age 45, unless they were 50 or younger, then you might need to start at 40 or younger.

Llor Exactly.

Hochster And they have a higher risk and need to do it a little bit more often, and that is something the family should know about.

Llor Exactly.

Hochster You said 15 to 20% of colon cancer is familial based, or has a genetic risk factor associated with it, what are some of those other families that need to be more concerned about the development of cancer?

Llor There is a smaller group, about 5% of all colon cancers that belong to what we call syndromes. Basically, what those are is different types of diseases that are due to a mutation in a particular gene that can be inherited from one family member from one generation to the next generation.

Hochster So if you like to blame your mother for everything that is wrong with you, in this case, you really cannot?

Llor Absolutely. It can be your father too. The chances are 50-50, and the bottom line is that those are cases that although are not a large portion of all colon cancers, they are very important because their cancer risk is extremely high, between 70 and close to 100%, for instance, in polyposis syndromes, so these groups do deserve very special care and in many cases now, the genetic defects, the mutations in the genes have been identified, so actually we can test family members

22:56 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

and make recommendations for cancer screening to individuals who have inherited the mutation and yet the individuals who have not inherited the mutation in that family, we can reassure them that their risk is not higher than average, so it really helps us a lot now.

Hochster So the great thing is we can actually test the DNA of all the family, just take a swab from their mouth and then if they do not have the gene mutation, if they did not inherit it, they are the same as everyone else.

Llor Exactly.

Hochster And if they do have it, we can watch them much more closely.

Llor And the beauty is that we have very good studies showing that watching them closely and doing certain preventive procedures, does save a lot of lives in a particular family, so it is not by any means a death sentence to have a syndrome like this, what it really tells us is that we know who has it, and diagnosing them is so important because we can make a huge difference in how they will do.

Hochster And one of the more rare ones is called FAP, is that right?

Llor Familial adenomatous polyposis was actually the very first familial colorectal cancer syndrome that was identified. Individuals develop many polyps at very young ages and if we do not remove the colon, basically almost everyone will develop colon cancer. This is not the most common one. The most common one would be Lynch syndrome and that is tougher to diagnose because these individuals do not develop a large number of polyps and therefore, the challenge is to distinguish them from the ones that are what we call sporadic, but those are most common cases that are due to inherited genetic defects.

Hochster So amongst people who are high risk for inherited genetic risk factors, the most common one for colon cancer is people who have Lynch syndrome and they can get other kinds of cancers too besides colon cancer, so what do we know about this Lynch syndrome?

Llor First of all, we do not like to call it a colon cancer syndrome, because as you said it is a multi-cancer syndrome. There is a very high risk of endometrial cancer, ovarian, and there are lots of other different risks or high risks of developing cancer. It is inherited from one generation to the next generation and you have 50% chances of inheriting the disease when mom or dad are carriers. All you need is a mutation in one gene. You do not need to have the two, what we call alleles, one always comes from mom, and one comes from dad. In this case, we only need to have one that is mutated and that will develop into these syndromes. In general again, the risk of cancer is high and there are some preventive measures and tests that actually are being performed in order to prevent those cancers in these families, but the most important thing

is diagnosing everyone who is susceptible to have them and do the right thing and the outcomes are really very different.

26:07 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

Hochster What is the specific thing that people inherit that gives them this syndrome?

Llor They inherit the mutation in one of the genes called a mismatch repair, so basically the DNA changes in our cells, they keep constantly making copies of DNA in our body, so what happens is that because this process is very fast, our body does make mistakes on a regular basis, but we do have a mechanism which is a group of proteins called mismatch repair proteins, and what they do is basically they recognize some of the mistakes that are made when we are making the DNA change and basically recruit our proteins and all of them work together to fix those mistakes.

Hochster So it is a little bit like having spell check on your computer and auto correct? It goes in there and fixes the spelling error.

Llor That is a very fair comparison, so when one of these genes is mutated, often what happens is that the protein that they usually produce is no longer produced and this protein, therefore, can do this job of fixing those mismatches. What happens is that then the mistake gets made and does not get repaired and everytime the DNA chain keeps making new daughter chains, these mistakes keep reproducing over and over and we end up generating lots and lots of mutations that when they fall in genes that control cell growth differentiation, they end up developing into cancer, so that is what happens with Lynch syndrome.

Hochster In these people with Lynch syndrome, we call it in the colon HNPCC, they have a higher risk of colon cancer, not everybody is going to get colon cancer for sure, but they have a higher risk and they need to have closer surveillance? And there can be cancers in other organs but colon cancer is the main one?

Llor Right, colon and endometrial will be the main ones. Colon is in between 70 to 80%. Information varies a lot depending on studies looking at large populations versus studies from high risk clinics, but in general, the highest risk would be for colon and for endometrial cancer.

Hochster And endometrial is from the lining of the uterus, so women need to be more concerned about that obviously, and that makes up what percentage of colon cancer?

Llor That would be between 3 and 5% of all colon cancers.

Hochster So most colon cancer is still this kind of what we call sporadic, it just happens because the DNA starts to go bad and makes a polyp and then eventually with time the polyp turns into cancer.

Llor Exactly, correct.

29:00 into mp3 file http://yalecancercenter.org/podcasts/2015%200315%20YCC%20Answers%20-%20Dr%20Llor.mp3

Hochster The job of the gastroenterologist when they are doing the colonoscopy for screening is to actually find the polyps and remove them and then you will not get cancer at all. Are there other familial syndromes that people should be concerned about?

Llor Lynch, as we said before, it is the most common syndrome, but we also know of some other colon cancer syndromes that look like Lynch but we do not know what is causing them, so there is a lot of research going on in those and then as we mentioned briefly before, the polyposis, we mentioned familial adenomatous polyposis, but there are others like one called MAP which is MYH associated polyposis, that is different from the rest of the colon cancer and most cancer syndromes because this is what we call autosomal recessive so you need to inherit one damaged genetic copy for mom and one from dad in order to end up developing the disease.

Hochster So that is much rarer?

Llor That is much rarer, exactly.

Dr. Xavier Llor is Medical Director of the Colorectal Cancer Prevention Program and Co-Director of the Cancer Genetics and Prevention 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, archive programs are available in both audio and written format atyalecancercenter.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.