

Welcome to Yale Cancer Center Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Center Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. March is colorectal cancer awareness month and this week our guest host, Dr. Howard Hochster welcomes Dr. Xavier Llor. Dr. Hochster is Professor of Medicine in Medical Oncology, Associate Director for Clinical Sciences at Yale Cancer Center and an expert in Gastrointestinal Cancers. Dr. Llor is Associate Professor of Medicine and Digestive Diseases and Medical Director of the Colorectal Cancer Prevention Program at the Yale School of Medicine. Here is Dr. Howard Hochster. Hochster Dr. Llor, tell us a little bit about how common colon cancer is and our general approach to diagnosis.

Llor Colon cancer is certainly common. It is the second most common cancer for both men and women in the United States and over the last few years, we have seen a nice decrease in the incidence of this cancer due to mostly the screening efforts that they have been happening in this country.

Hochster Most people do not like to think about their colon, yet alone the waste products of their colon, but can you tell us what do we mean by screening, I mean is it like rectal examination, do I have to handle my stool?

Llor There are several approaches to colon cancer screening. Basically, the important thing to know is that colon cancer is a slow growing cancer. On an average, it seems to take about 10 years from the beginning with a small tiny polyp to a big polyp that grows into finally a well-developed cancer, so there is a long window of opportunity for us while we are screening to detect those tumors early enough and thus decrease the risk of colon cancer. There are several approaches to colon cancer screening. The most widespread approach is colonoscopy, at least in this country. There are others, which is basically passing a flexible rubber tube with a camera on the tip that we go through around the entire colon and if we see these polyps that usually are the early lesions, we can remove them on the spot with a colonoscopy but there are other options, some of them based on stool test and some of them are newer than others and that is an appealing way of screening for individuals who are not interested in more aggressive kind of testing and there are already some blood tests that have not been that well validated yet, probably they will get perfected and may be in the future will be able to screen with just a blood test but this is not primetime yet.

Hochster I have seen some ads on TV where they have a happy colon and a box that goes off to the laboratory. What are those tests?

3:34 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 Llor Right, those are the tests that basically what they do is they have a combination of the old occult blood test plus a molecular test, so it is a little bit of an enhanced version of the old stool test with the slightly higher detection rate for particularly for colon cancer and

advanced polyps.

Hochster So, if I send my stool off to get tested that way, they are going to look for some DNA that falls off these polyps or the colon cancer into the stool and that would tell us that it is a high likelihood there is a polyp, so after that I would still need a colonoscopy right.

Llor It is more than a screening, probably the way to see it will be a pre-screening test because the positive ones will be the ones which we will be recommending for colonoscopy and the negatives ones, we will be recommending to repeat the test right now every 2 to 3 years, may be 1 year, it depends, it is still unclear.

Hochster So we know that colonoscopy really helps reduce the rate of colon cancer right?

Llor Yes.

Hochster There have been some large studies where people either got colonoscopy or kind of regular other stool testing and so forth that have really showed it can reduce the risk of colon cancer, so I would like to tell people that it is really important to have the screening tests because colon cancer is largely preventable, I mean, most colon cancers start with a polyp that you can pick up within the first couple of years, so that is the key thing. If you go for screening testing for colon cancer, you should be able to avoid getting colon cancer and the earlier we find it the more likely it is to be cured; at stage I, you know, surgery alone is probably more than 90% effective at curing people from ever having to deal with it again, so that is why we want people to go for these tests even though there are some issues involved with it like preparation for the colonoscopy, so what is involved with that?

Llor In order for a colonoscopy to be successful to see all the larger and smaller polyps, the colon needs to be clean and truly the best way to clean a colon is through flushing quite a lot of volume of liquid through it, so that is the preparation. It is about 1 gallon, now we are doing in split, half and half, the day before the procedure and day of the procedure but bottom-line is we do need a lot of liquids going fast through the colon to clean it up from any particles, so we can get to see that colon well and therefore for the test to be really successful so that is probably the most annoying part of the colonoscopy, the preparation for it.

6:37 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 Hochster The last time I went, you are spending the night before in the bathroom, but when I went for the colonoscopy, I went to sleep basically.

Llor Right, it is done either with conscious sedation or anesthesia in all cases, it is a pleasant experience once we are there and we pretty much do not recall anything, so again I think the hardest part is truly the preparation and not the procedure on its own.

Hochster So who is supposed to get screening tests for colon cancer and screening colonoscopies?

Llor So in general for everyone, colorectal cancer screening is recommended starting at age 50, in several societies I have also recommended starting at 45 for African-American because of the highest incidence of younger individuals diagnosed with colon cancer and so start at age 50 for absolutely everyone, males or females and individuals with family history or other circumstances, they may require earlier testing but that is what we do tailor recommendations specifically for these individuals but in general overall for individuals who have no family history, age 50 will be the age to start and 45 for African-Americans.

Hochster But if your parent had colon cancer or your brother or sister, then we want you to start earlier, like age 40, more or less.

Llor In general, we start earlier, 40 or 45, but if they were early enough, we usually do it 10 years before the diagnosis of that family member, so we really look at what happened to family in terms of deciding when the patients need to get started with a colonoscopy.

Hochster Well, so your particular area that you are the big expert in relates to inherited problems or genetic abnormalities that lead to colon cancer, so what are common family syndromes and molecular changes or genetic changes that people get that lead to colon cancer and what do we see with those families?

Llor Right, those cases are about 5% of all colorectal cancers but again because colon cancer is that common, there is plenty of those cases too. In general, we divide those syndromic cases which means that the individuals have mutated gene and that is passed generation after generation and that is a predisposing condition to colon cancer and in many other cases other cancers too and in many other conditions too. In general, we divide it between the ones that cause a lot of polyps and the ones that really do not cause polyps and all but cause just heavy development of very fast cancers. Those non-polyp ones, the common one is Lynch syndrome; when it comes to polyposis, ones that we call polyposis because individuals develop a significant number of polyps with several of them, the first one is familial adenomatous polyposis but now

10:05 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 we have over the last few years, we have learned several more like MAP or MYH-associated polyposis or PPAP or polymerase proofreading-associated polyposis, so we over the last few years have learned of several more genes and genetic defects that also cause this syndrome so the menu has grown a little bit, though again they are about 5% of all colorectal cancers.

Hochster So, 95% of colon cancers are not familial sporadic but the most common one in their 5% is Lynch syndrome or what we call HNPCC, so can you tell us a little bit more about people who have these things in their families, they tend to know it for the other ones because they cause a lot of problems

for many people in the family but there is some sporadic Lynch syndromes or people who really do not know that they have it right?

Llor Yeah, you know in general, the challenge always with these cases where there is no polyposis is that if we do not think and we do not ask about family history, often we miss those, it is much when we see cases with polyposis, when we see many polyposis, it is hard not to think about cases like this but in nonpolyposis cases like Lynch syndrome but we often just do not spend enough time asking about family history or we do not really pay enough attention and we may miss those cases. There are several approaches, one of them is truly making sure that we get good family history from everyone and also nowadays there are some 2 more testing that is done systematically that really helps us prescreen for individuals with Lynch syndrome and that is something that is becoming widespread and available in many hospitals.

Hochster So who should be more aware or like if we ask a question if there is Lynch syndrome in their family like what kind of characteristics do the Lynch families have that might raise somebody's awareness that they need to look into this?

Llor Sure, in general, it is families that have several members with cancer and it not only colon cancer but endometrial cancer is very common too and then also some other types of cancer, ovarian, pancreas, and again most of these colon cancer syndromes are not truly colon cancer syndromes but are multicancer syndromes because they also increase the risk of other types of cancer, so really any family with several members with different types of cancers, we should just make sure that we are not missing on anything, some of them would be less likely, some of them are more likely to be associated with Lynch syndrome, that is why it is important to really pay attention to all the cancers. Some of them often develop earlier than usual but not all time we see a lot of Lynch syndrome families who have done really well with cancers that early in life, yet they still have many family members with cancers.

12:58 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 Hochster So, if you have multiple cancers in your family in more than one generation and some of the people are under 50 or younger, those are the ones that we should be particularly looking into their genetics.

Llor Right, those are the ones that we should never be missing but those are not in great majority. We often see families where we do not see that many members who are that young and that is also part of where we live right now. Families are much smaller than what they used to be. Therefore, the number of cancers may not be that big yet there are some cases that should make us suspicious. Those cases that have young individuals definitely we should not be missing them but when we see several cancers in a family, we should always raise a suspicion or at least think about it and see if it is a consideration for them to be part of the syndrome.

Hochster We are going to take a short break for medical minute. Medical

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The American Cancer Society estimates that there will be over 75,000 new cases of melanoma in the US this year with over 1000 of these patients living in Connecticut. Well melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. When detected early, however, melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center at Smilow Cancer Hospital to test innovative new treatments for melanoma. The goal of the specialized programs of research excellence in skin cancer or SPORE grant is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improve diagnosis and treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital. More information is available at YaleCancerCenter.org.

Hochster Welcome back to Yale Cancer Answers. This is Dr. Howard Hochster and I am joined tonight by my guest, Dr. Xavier Llor. We are discussing screening and prevention for colorectal cancer. So, Xavier I think in the first half we talked about screening that it is important for people, we recommend everybody starts getting screened at age 50, I mean what percent of colon cancer, if everybody went for colonoscopies, could we really prevent colon cancer entirely?

Llor I think some of the studies that have addressed this and have projected that probably it could avoid about 80-85% of them. Some of them, we are still having a hard time.

16:10 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 There are some cases for instance that were cancers that grow from a very flat surface, not like these polyps that we have in mind, these mushrooms that we have in mind, therefore, some of those are very difficult to detect. Colonoscopy is not perfect to the colon. It is made of folds and the colon keeps moving, so sometimes we may miss on some particularly, small polyps but sometimes even larger ones, so while colonoscopy is the gold standard in terms of visualizing the colon, we still have some limitations and we have to assume that sometimes we may still miss things even with such a good test such as colonoscopy.

Hochster So, colon cancer is the third most common cancer in United States today in both men and women and so I think there are around 60,000 to 70,000 cases a year in the US so we could really get that down to 15000 probably if everybody got screened appropriately.

Llor To tell you the truth, if we compare with all the other types of cancers,

that is probably one of the cancers that is more preventable, the opportunity here is great and I think that we see clearly the results of that push for screening with the incidence going down every year since the late 1980s and more so since the generalization of screening strategies. Certainly, I think it is a success story.

Hochster So, unlike some other cancers where there is still a question if you know certain kind of x-rays, mammography, CAT scan for lungs, I mean there is a lot not known about how effective screening is for other cancers. We know that colonoscopies prevent colon cancer from ever forming and that is because it takes a few years to go from the polyp to the cancer stage and you actually remove the premalignant lesion, the polyp, when you do the colonoscopy, so you are getting both things at once and I think that is one of the key things about it. Unfortunately, as I said previously, it is a little hard for people to deal with the whole issue of their colons and clean out some things like that but you know we want to keep working on this and keep making it easier, so what do you see coming along in the way of screening, I mean are there you know 10 years from now are we still going to be doing the same kind of things for screening?

Llor I believe that probably we will have a pre-screening tool that is better than what we have right now and our first approach probably will be a blood test and for the positive ones that will go over to colonoscopy, I will not be surprised, so these will be basically and if we have some premalignant cells that are already developing down there hoping that some of those go to the blood stream and we are capable to detect those changes then use them as our prescreening tool, I would think that is reasonable.

Hochster So you kind of rely on the cancer to leak out small pieces of mutant DNA, the problem is that it is very small in small quantities and we need to be able to detect

19:44 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 quantities at a lower level than that are really applicable today, but we are making a lot of progress in ways of detecting small amounts of cancer. I mean we are kind of getting to the point in people who actually have advanced cancer that we can follow DNA changes to understand the response to treatment but probably it has to be 100 or 1000 times more sensitive to be a good screening test.

Llor Right, but I think challenges are there but I think that when we see the progress that has been made in terms of availability to detect really is tiny amounts of DNA for instance I am very hopeful that we will see these not in a very long time.

Hochster Well I guess everybody will be happy to get away from sending their stool to laboratory, so that would be a lot better. What about prevention, do we see a role for prevention in the way of colon cancer development, ways people who are at risk taking some things, so they will have a lower risk?

Llor I think that this is one of the aspects that we will have to work very

hard and there is certainly a push for instance by the American Cancer Society and all that in both primary prevention and chemoprevention. When it comes to primary prevention, those are simple things that at the end of the day are not that easy to modify exercise a balance diet, absence of toxics like smoking, although seem to really carry a heavy weight in terms of the number of cancers that we develop, we just need to compare the incidence of countries where these factors are better checked than here and we see that actually the incidence goes up in most places where we start becoming more obese and we exercise less and so that would really help prevent a lot of cancers and I think the primary prevention is important and we really have to keep working on that not only for colon cancer but for other cancers. Then we have the other issue which is the chemo prevention.

Hochster A few years back, they were saying more fiber in your diet like the bran muffin for breakfast, that is not part of it anymore?

Llor I think that when we talk about diet as a whole, if we have more fiber, probably we have less fat because we are not eating more of everything and I think it is a matter of truly finding a right balance and the right balance I think is nothing mysterious right now, less red meat, more fruits, more veggies, all these stuff, it is not only good for colon cancer for our heart but also for other cancers, so I think that it is really the right mix and exercising more, being more active and less sedentary and less smoking and all those things, at least from what we know should have significant impact on risk down the line, so we really have to make a big effort in trying to really go towards more healthy lifestyle.

23:08 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 Hochster It seems like exercise is very helpful. We see that as preventive today in trials with breast cancer, colon cancer a little bit but there is a big study going on in Canada and for people who have already had a colon cancer removed in all the trials that have been done to reduce the risk of recurrence, exercise seems to help, so that seems to be a pretty consistent theme if you exercise an hour 3 times a week that seems to provide enough. Do you have any idea what is happening when we do that exercise in these settings, how is that helping prevent these scans?

Llor I really do not have good knowledge of what can be happening exactly and what is the mechanism but certainly there are issues about body fat deposits. There is also this issue about kind of chronic low level inflammation sometimes that comes with obesity that is associated with less exercise, so maybe there are several factors, not only one factor but bottom line is you were saying it does seem to make a difference even at levels in individuals who already developed a cancer, so certainly, we have a big task here to really promote healthy lifestyle in order to really prevent cancers in general.

Hochster Yes, that does seem to be a very good strategy, so I wanted to go back to a minute for we were talking about genetic syndromes and cancers that run in the family, so the most common colon cancer syndrome is what we call Lynch

syndrome or hereditary nonpolyposis colon cancer, HNPCC, in that syndrome you inherit DNA repair defect from a parent, basically the way I would like to tell patients about it is that your spellchecker for DNA is not working right and you have a lot of misspellings, so that leads to DNA mutations. We are actually screening for that all the time in people who have colon cancer today right?

Llor Yes, absolutely and that is also made a big difference, so there are several genes that we know are responsible for Lynch syndrome. In all these genes, every gene does produce a protein, so when we have a mutation in any one of these genes, the protein is not produced and that can be seen very easily through a test called immunohistochemistry, these types of tests are done all the time in pathology labs, so nowadays, through the recommendations of several guidelines, many hospitals including ours do colon cancer screening and in many cases like ours do endometrial cancer screening, so every time a tumor from the colon or endometrium comes to the pathology lab, they run these tests and if they see absence of any one of these proteins, then there is a suspicion for Lynch syndrome and that is when we undergo evaluation and see if there is actually a mutation underlying that defect, so that is a good way to really pick up cases that otherwise go missing because of the problem we are saying before that we often we do not think about those cases, so it has really become a very useful strategy to really identify families with such a condition.

26:38 into mp3 file https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0305-Podcast-Llor_295849_5.mp3 Hochster And those who actually treat colon cancers are very interested in this too because it looks like that group that has these protein deficiencies, a mismatch repair proteins, they tend to be more treatable with immunotherapy drugs as opposed to chemotherapy drugs, so that is kind of really interesting emerging story but for this purpose anybody who has colon cancer anywhere today at major centers their cancer will get checked for these enzymes. Sometimes, they are not inherited. They are some that we call sporadic but most of the time they are inherited and that could be seen again in multiple first-degree relatives in more than one generation, so if you are young, if you have colon cancer on the right side, near the beginning of the colon or what is called the cecum, part of the colon, those are people who tend to have these Lynch syndrome tumors generally though not exclusively, but these are the questions that people need to ask if they fall into those categories I think.

Llor Absolutely, in general, for instance when it comes to side of the colon where colon cancer happens, 70% of the time in the sporadic population, it happens on the left side of the colon, yet in Lynch syndrome, it is about 50-50, so there is an important shift towards the right side of the cecum, so those are also clues that help us to really assess risk for genetic defect.

Hochster And if you think that that is what is going on then we would like to refer people to the genetic counselor so they would see people in your area and what happens then when they go for genetic counseling.

Llor So basically when patients are identified either this way or through family history, then they are seen in cancer genetics and basically there is a family pathway that is created with the information of the entire family to really help us assess what is happening. We look at the information on the tumor also if we have that information too and if that patient does look suspicious, then we would proceed with genetic testing which is done through a blood test and sometimes through a saliva test only and basically that way we can really see if the genetic defect is identified. If that is identified, then all family members can be tested for that mutation which really help us identify who has predisposition to cancer in that family, so those are the individuals who we will be following very closely. Dr. Xavier Llor is Associate Professor of Medicine and Digestive Diseases and Medical Director of the Colorectal Cancer Prevention Program at 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. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on WNPR, Connecticut's Public Media Source for news and ideas.