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 liver cancer with doctors Amy Justice and Tamar Taddei.

Dr Justice is the CNH Long professor of Medicine and Doctor Taddei is associate professor of medicine at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology. So maybe I’ll start with you doctor Taddei, tell us a little bit more about yourself and what you do.

So I’m a hepatologist and my research focuses on outcomes in liver disease and liver cancer as well as in clinical trials and prevention and detection of liver cancer.

So that’s sort of me in a nutshell. What about you doctor Justice? So I’m a clinical epidemiologist and I have spent my career harnessing the national electronic health.
record system that the VA has to try to study important clinical phenomenon like liver cancer. Also, HIV, hepatitis C, and a number of other conditions using that national database. And so I mean, it seems like the two of you would have obvious research synergy, but one of the things that’s always exciting and interesting to me is to see how people from arguably different fields. One an epidemiologist 1A hepatologist kind of collide to come up with interesting research ideas. So I wouldn’t call it a collision. I actively sought Amy’s mentorship so Amy has more than 20 year history of developing cohorts in the VA in VA. Data to carefully develop clinical phenotypes of disease specifically around HIV and aging, and many other diseases. Because a lot of this work in HIV patients has also, you know HIV patients commonly have hepatitis C, for example. They commonly have metabolic disorders.
And so she’s really built a research environment that can study systems related diseases in a way that was incredibly intriguing to me. As a young person who wanted to develop a cohort of patients with cirrhosis at risk of liver cancer. And so I sought her advice, and this was in somewhere around 2011, 2012. I asked to meet with her and I said, I’ve I’ve seen your work. I think I’m going to need a lot of handholding, and there began a decade of a phenomenal mentorship for me, so that’s how we met. And doctor Justice tell us a little bit more about kind of the ideas that were generated. The projects that you’ve designed, and what the Genesis was of that. Well, I’m a general internist, so I think broadly, which is sort of complementary to being an epidemiologist because epidemiologists also think fairly broadly. But I realized early on that I could not be an expert in every one of the conditions that were worthy of study using the VA data,
so I've always had my eyes out for a young promising people who want to be the experts in those particular domains and tomorrow absolutely fit that Bill. And part of what I think is really exciting about doing this work is that there are a number of cores and work groups affiliated with the cohort studies that I’ve created, and each one of those cores in workgroups has greater depth and understanding of the clinical questions that they are looking at than I do. But what I offer is sort of the connectivity among those groups so that we can learn how to do a phenotype once somebody develops diabetes in the endocrine group and we can use it in the liver group without having to recreate another wheel so that we are definitely more as a. We are more than the sum of our parts and I find that exciting and a lot of fun coming into work every day. So just for people who are not familiar with your work when you’re talking about these different cores and kind of spanning research phenomena across different groups, tell us more about how that exactly works. Can you contextualize that for us and
maybe give us a specific example? Sure, so I’ll talk about tomorrow’s work because that’s most relevant to this.

Call so when Tamar came to me initially she wanted to create her own cohort study, which she did with aplomb. But then, over time,
she realized that she could also benefit from doing some analysis with some of the databases that we had created. The cohorts we created that were a little bit more generic than only people who had cirrhosis per se. Not to mention that we had other data that we had merged into our cohort studies that wasn’t yet available to her in the other study. So she wrote up a proposal, which was a brief outline of what she wanted to do.

I reviewed it, thought it had the critical information that we needed it, and then it went to the liver core, which is a standing group of people who are very interested in liver research in the VA data bin. Lorry is the head of that core, along with Jan Tate, who is the Methodologist Ben Larae being the clinician.
They reviewed it. They made suggestions to her. Several people in the course said they were interested in participating and signed on to be on the writing committee and we went from there. And so doctor T tell us a little bit more about the questions that you were trying to answer with these studies. So the first question was really how to understand via data. So where do you go to develop a cohort? How is it housed within the you know V8 computing infrastructure? How do you actually look at that data in a way that makes sense and ask the right question? So just having the data doesn’t really lead you to the right endpoint. You have to actually start with a good question and sometimes. Good questions actually require a lot of effort to actually be able to define your population properly, and so in the beginning when we set up the cirrhosis cohort, which is called the vocal cohort, I did this with my colleague Dave Kaplan at Upenn. There’s a lot of parallels between Upenn and Yale,
A lot of collaboration going on there, and so we actually had to really define severity of liver disease in that cohort, which is hard to do, and we took a lot of advice from Amy and from then and how to do that and so since the inception of that cohort, we set that cohort up in 2012. We've published some probably 25 papers now on cirrhosis and outcomes in cirrhosis from everything to important clinical questions around the use of anticoagulants in these patients to the burden of cost of liver cancer. Care to you know, all kinds of different questions that are that are answered in a large cohort, but I think one of the issues that’s very important is that when you develop a population cohort, you make a lot of assumptions, right? You say, well, I’m going to be looking at people with cirrhosis, right? And yet, cirrhosis happens over decades. There are many risk factors that lead to cirrhosis, and while cirrhosis is the single most important risk factor leading to liver cancer,
I wanted to have a better idea of what happens to people before they develop cirrhosis. And are we missing upstream risk factors? Perhaps by selecting this population and because I'm not an epidemiologist, I really rely heavily on Amy's Broadview because you know, the more specialized you become in medicine. The more blinders you have and and sometimes you need somebody to sort of shock you into saying wait a second, don't look at that population. Look at the whole population and let's think about this rationally. And so in in more recent work we've been looking at the whole VA population to look at upstream risk factors for liver cancer and what was important about that was the realization that if you only if you looked at cirrhosis and put that in as the risk factor, it washed out. All the factors that occurred before cirrhosis occurred, yet cirrhosis is hard to reverse whereas fatty liver diabetes can be addressed more effectively.
So it was very important to look at the whole population and begin to look at upstream phenomenon like tomorrow was talking about. Yeah, I mean, it seems that there’s a very heterogeneous population that kind of all leads to the same endpoint of cirrhosis.

So tomorrow maybe you can tell us a little bit more about. The epidemiology of cirrhosis and of liver cancer. How common is this anyways? So cirrhosis is actually quite common. And liver disease in the general population is also quite common, so there’s at least thirty million Americans living with liver disease with known liver disease. And there’s probably many more millions that are at risk for liver disease and don’t know it. OK, so the major risk factors for liver disease are viral, hepatitis, hepatitis B&C, alcohol, excessive or unhealthy alcohol use and then.

What we call fatty liver disease, which can be alcohol associated and non alcohol associated and that’s part of a bigger metabolic syndrome that we actually see being sort of
a canonical risk factor for cancers. All kinds of cancers in fact, and our epidemiology in liver disease and liver cancer is shifting fairly quickly because we now have a cure for hepatitis C. And so while hepatitis C dominated as a risk factor in the US for many decades. We’re able to cure it now, and we’re actually seeing more obesity and alcohol associated liver disease and liver cancer coming to the fore. So these are major public health issues that really need to be addressed at a national level. And so Amy, when you think about you, know fatty liver and obesity and alcoholism. What proportion would you say of the VA cohorts or of the cohorts in general that you’ve looked at are at risk of one of these such that you really wanted to look at the global population? At least 1/4 I’m depending on and depending on how you define it more, possibly even up to half. And for all of those people is the mechanism and the endpoint of cirrhosis the same? In other words, both from a molecular standpoint that you know there...
is some sort of liver injury that essentially then results in cirrhosis. As well as the degree and the type of cirrhosis, are those of the same whether you happen to have gotten to that endpoint through obesity versus a hepatitis E versus alcoholism. I’m going to let tomorrow address that ’cause she spent a lot of time on that and it’s a beautiful question. So I think the question is, do you want to make things sound simple or do you want to just embrace the complexity that’s there? You know Amy’s always telling me. Just embrace complexity, right? And it’s true. I think cirrhosis is a final common pathway of all of the Cascades that lead to liver injury and repair and aberrant repair. You know, Yep, you can call cirrhosis the final common pathway, but that tells you very little about all of the Cascades that happen to get there, and I think actually we need to look at liver disease and liver cancer from an ideological standpoint. Meaning what is it? What’s the etiology or the
ca’ cause that brought you here?
Because there are different molecular
sort of biologies of those pathways
and then the cancers themselves.
You know,
even though we think about
two sort of dominant.
Primary liver cancers.
The 90% of these liver cancers
are are termed hepatocellular
cancer and they arise from the
liver cell from the hepatocyte.
But they look totally different
under the microscope.
So that begs the question,
are we dealing with so much
heterogeneity here that we’re just
lumping these things into one name?
Liver cancer?
Yeah, so you know I really want
to dive more into liver cancer.
The different types of liver cancer.
Whether the etiologies of these
cancers actually play a role in
terms of prognosis and treatment and
where things are going in the future.
But right now we have to take a
short break for a medical minute.
Funding for Yale Cancer answers
comes from Smilow Cancer Hospital
where integrative medicine services
help patients navigate physical, mental and spiritual Wellness during and after cancer therapy. To learn more, visit yalecancercenter.org integrative. The American Cancer Society estimates that over 200,000 cases of Melanoma will be diagnosed in the United States this year, with over 1000 patients in Connecticut alone. While Melanoma accounts for only about 1% of skin cancer cases, it causes the most skin cancer deaths, but when detected early, it is easily treated and highly curable. Clinical trials are currently underway at federally designated Comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital. To test innovative new treatments for Melanoma, the goal of the specialized programs of research excellence and Skin Cancer Grant is to better understand the biology of skin cancer. With a focus on discovering targets that will lead to improved diagnosis and treatment. More information is available at yalecancercenter.org you’re listening to Connecticut Public Radio. Welcome back to Yale Cancer answers.
This is doctor a nice check part and I’m joined tonight by my guests, doctor, Amy Justice and Tamar Taddie. We’re learning about liver cancer treatments and research, and before the break we were talking a little bit about cirrhosis and the different pathways that people can get cirrhosis. But I thought maybe we’d start first with thinking about, you know, doctor Justice. Do all cirrhotics get liver cancer, and does all liver cancer come from cirrhosis? So the answer is that not all cirrhotics develop liver cancer, but cirrhosis by itself has a pretty poor prognosis associated with it. You want to avoid cirrhosis if at all possible. And it is possible to develop liver cancer without cirrhosis. Most classically, if you have hepatitis B viral infection, you can go directly to liver cancer without passing through cirrhosis. But more typically the vast majority of people who develop liver cancer have had cirrhosis previously and doctor Taty.
If you have cirrhosis, how is cirrhosis diagnosed so cirrhosis has to be suspected and that’s the problem. So your liver is your largest solid organ and it regenerates, which is marvelous. But it doesn’t tell you it’s sick until it’s very, very sick, and that’s a problem. We would love to detect cirrhosis in that early stage where patients don’t feel any different and their counts are still OK, and there’s still more or less healthy. But more often than not, we detect cirrhosis when people present with signs of early liver failure, like jaundice or bleeding or very low platelet counts. This is already very, very advanced and it very much limits what we can offer that patient in terms of treatment. If they do have a liver cancer. All patients with cirrhosis should have screening for liver cancer in the form of an ultrasound every six months. And it’s really important to talk to patients about the fact that your body may have problems even if you don’t feel it. And I think this is something that people have a hard time wrapping their
head around that you could actually be harboring a chronic illness and really not notice any change in how you feel. Which is why people really do need to go to the doctor regularly. It’s an important thing to have a physical and to have an established rapport with a primary care doc who knows you and has looked at you over time and can see subtle changes when they come up before you even feel them. Doctor justice talk a little bit more about that. I mean, we talked about some of the things that can lead to cirrhosis, and I think some of us might be thinking. You know, maybe I am a little bit overweight. Maybe I do enjoy a couple of drinks every now and then. If these are factors that potentially can lead to cirrhosis, and cirrhosis is silent except for when it’s pretty late and can affect my blood work, how is that diagnosed? I mean, should should I be going to the doctor and getting an ultrasound of my liver to see if I have cirrhosis? And would cirrhosis even show up on an ultrasound or a CT scan? Well again it depends on at
What stage you’re talking about.

So very early signs of liver injury that could lead to cirrhosis and may maybe an early harbinger of cirrhosis is the ratio of AST aspartate transaminase to alanine transaminase and platelets, which is also called FIB 4, and that’s a very routine test of patients. Get it very frequently when they see their doctors. It’s part of the the routine panel of tests that are sent for blood work. And if that test is abnormal or not rock solid normal, then it would be very reasonable to have a conversation around.

Well, how much do you drink? How long have you been drinking? OK, let’s look at your BMI, which is an indication of what your risk for fatty liver disease might be.

What’s your family history? You know those sorts of questions can be explored, and if enough of them are positive, then yes, an ultrasound would make some sense. I’ll let tomorrow talk a little bit more about what would happen when I refer the patient over after.
but as the primary care doc. Yes, I would consider getting an ultrasound on someone who I considered to be at high risk. So tomorrow just to kind of pick up the conversation there. One of the things that you both mentioned was that cirrhosis in and of itself is not something of itself is not is not something that you should aspire to have. I mean, not only does it increase your risk of of Patoc cellular carcinoma, but in and of itself. It can have problems. You mentioned that the liver was an organ that can regenerate. If you do have cirrhosis. If your blood work is abnormal, is there a way that you can reverse that? Can you lose weight? Stop drinking, you know you mentioned drugs that can cure hepatitis C. Now, can that reverse cirrhosis? Or is it the case that once you have a cirrhotic liver? You have a cirrhotic liver. It depends on how significant the scarring is of the liver. So very, very early cirrhosis.
We’re beginning to think more and more can be reversed if you take away the whatever is insulting the liver, right? So if it’s viral hepatitis you treat the hepatitis. If it’s alcohol, you stop drinking. There are people who can have their fibrosis reverse even very, very early cirrhosis. But once you have a lot of scar laid down and a lot of thick trabeculae we call them sort of thick bands of collagen deposition in the liver. The liver really can’t repair itself anymore, and so there is. There is a point at which you cannot turn back the clock, and so Amy, from an epidemiologic standpoint, and we we kind of touched on this a little bit before the break, but I just want to unpack it a little bit more. Is the rate at which you develop cirrhosis. If you have had any of these different. Sources of injury, whether it’s alcohol, whether it’s a hepatite E, whether it’s. You know being obese is the rate at which you develop cirrhosis, different in in those different etiologic factors and is the potential to develop hepatocellular carcinoma based on those.
Our priority risk factors different amongst each of those risk factors. So obviously drinking a little alcohol versus drinking a lot of alcohol is going to influence how quickly you might develop cirrhosis. You know if you are drinking extremely heavily cirrhosis can occur much earlier than if you're drinking fairly heavily for a longer period of time. We actually have studied this in HIV, which is a risk factor also for cellular cancer. And we were able to show using the VA data that people who were able to suppress their HIV get their virus undetectable. Had a much slower progression to hepatocellular cancer than the people who were not. So I think that's actually a pretty good template for a lot of these phenomenon. If you can manage these risk factors, try to get them as low as possible. You can modify how rapidly someone is going to develop cirrhosis, and that's a very important modification in terms of their risk for hepatocellular cancer. So do we know just to follow up on that? Amy, do we know, for example,
that whether if you have a history of hepatitis C that’s worse in terms of developing Cirrhosis and subsequent Patologia. Then, if you were a heavy drinker or you know, being a heavy drinker is a little bit worse than having a BMI of 30 do. Do we have any kind of ideas about the relative risk of each of these risk factors? So hepatitis B is probably the strongest individual risk factor. Thankfully, the prevalence of hepatitis B in the United States is relatively low. When you talk about things like hepatitis C, alcohol, fatty liver HIV, it’s not one size fits all. It really depends on how severely you have those problems or conditions, and so it’s not true to say that one is much worse than the other. It really depends on how out of control they are. Yeah, and so Tim are picking up on what Amy had kind of lead us to. You know if you’re referred to patient who’s got a suspicion for cirrhosis, they come to you and they’ve had an ultrasound or a CT scan. What’s the next step in terms of you know, checking to see whether they
0:24:08.2 → 0:24:09.538 have hepatocellular carcinoma?
0:24:10.19 → 0:24:12.422 So if they come to me with an ultrasound,
0:24:12.43 → 0:24:14.53 usually that ultrasound is sufficient
0:24:14.53 → 0:24:17.838 to look for large tumors in the liver
0:24:17.838 → 0:24:19.888 tumors over 2 centimeters, for example.
0:24:19.888 → 0:24:22.47 But we know that ultrasound in and of itself
0:24:22.47 → 0:24:24.684 is a very insensitive screening modality,
0:24:24.69 → 0:24:27.178 which is why there are studies underway to
0:24:27.178 → 0:24:30.107 look at more sensitive screening modalities.
0:24:30.11 → 0:24:31.93 When I'm refer to patient,
0:24:31.93 → 0:24:34.216 I actually think very carefully about.
0:24:34.22 → 0:24:35.52 What brought them to me?
0:24:35.52 → 0:24:38.22 So I think about viral,
0:24:38.24 → 0:24:40.075 metabolic and inherited disorders of
0:24:40.075 → 0:24:42.769 the liver that can lead to cirrhosis
0:24:42.769 → 0:24:44.739 as well as autoimmune disorders.
0:24:44.74 → 0:24:46.92 So I think you know,
0:24:46.92 → 0:24:49.08 cirrhosis is stigmatized because people
0:24:49.08 → 0:24:51.24 associate it entirely with alcohol.
0:24:51.24 → 0:24:53.532 And actually there are many different
0:24:53.532 → 0:24:55.939 causes of cirrhosis and even alcohol.
0:24:55.94 → 0:24:57.308 Some people can drink very heavily
0:24:57.308 → 0:24:58.6 and never have liver disease.
0:24:58.6 → 0:25:00.292 And some people can drink fairly
0:25:00.292 → 0:25:01.89 modestly and get liver disease.
0:25:01.89 → 0:25:03.126 So I think you know there
0:25:03.126 → 0:25:04.32 really should be no stigma.
0:25:04.32 → 0:25:05.247 Associated with cirrhosis.
0:25:05.247 → 0:25:08.136 So I I look at all of the sort
0:25:08.136 → 0:25:09.776 of pathways that could have
0:25:09.776 → 0:25:11.799 gotten them to where they are,
and then we usually in the liver clinic now have non-invasive ways of testing the liver stiffness which is a marker of how fibrotic the liver is and those ways of measuring are called transient elastography where we measure the stiffness of the liver and can give the patient right there an estimation of how serious this may be, and then from there I try to figure out if there’s anything I can help remove that could be stressing the liver, and so there are some treatments for some of these different causes obviously, and then you know they I make sure I go over what we call cirrhosis, health maintenance with the patient, you know what they can do to protect their liver, how often they need to be seen, how to protect themselves against other illnesses, because when the liver has cirrhosis it sort of loses a lot of its immune surveillance ability for certain pathogens. You know they need to be up to date with their adult vaccines, that sort of thing.
And then you know if the liver disease is very severe. We talk about things like liver transplantation. And certainly if the patient comes to me with liver cancer, as many of my patients come to me with, you know, newly diagnosed liver cancer, that’s a whole other conversation around prognosis and treatment and all of that. So, so in our last minute, maybe we can just talk a little bit. About prognosis and treatment of liver cancer tell us more about how that’s treated and and what the prognosis really is. Well, this is really tomorrow specialty, but unfortunately because people present so late the prognosis is quite grim. With that I will hand it over tomorrow. So tomorrow are there new treatments that can make that prognosis less grim? Yes, so in the last five years we’ve seen a number of new agents come to the market for advanced liver cancer. We’d still really like to detect liver cancer at its earliest stages, where it either can be removed by surgery or treated ablative Lee.
And so I think it’s important to really raise awareness for people to get screened if they have been diagnosed with cirrhosis. Certainly we’re always looking at screening and risk factors, and whether there are other things apart from cirrhosis that would bring a person to screening. Like chronic hepatitis B for example, but the treatments are dependent on stage and the overall survival in liver cancer is about 18% at five years, which is dismal. But it’s getting better because we have new agents, things that can really change the course of a patient’s life is, you know, surgery to remove the tumor, but also liver transplantation in patients who have liver disease and are perhaps too sick for those surgeries. And so you know, there are a number of different local treatments that can be done for sort of what we call intermediate disease. But the most important thing is for the patients case to be discussed in a multidisciplinary tumor board, because there are many people who manage liver cancer and we all need
to come to the table to develop a clear plan for the patient. And you know, to really think about that, patient their unique circumstances and what’s best for them.

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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 funding for Yale Cancer Answers is provided by Smilow Cancer Hospital and Astra Zeneca.