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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer 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. This week, Dr. Gore is joined by Drs. Amy Justice and Tamar Taddei for a conversation about liver cancer in an aging population. Dr. Justice is Professor of Medicine and General Medicine and of Public Health and Health Policy at the Yale School of Public Health and Dr. Taddei is an Associate Professor of Medicine in Digestive Diseases at Yale School of Medicine. Dr. Gore is Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore Could you both tell me a little bit about what it is you do? It sounds like you are both at the Yale campus, but also at the VA?

Taddei I am a hepatologist.

Gore A liver doctor.

Taddei I am a liver doctor, yes, and I practice mostly at the VA. I do see patients at Yale, but the core of my practice is at the VA dealing mostly with veterans who have liver disease and specifically veterans with end-stage liver disease and liver cancer.

Gore And end-stage liver disease, is that cirrhosis mostly?

Taddei Correct.

Justice I was section chief of general medicine at the VA for about 10 years. I have since stopped doing that and do research almost full time, including mentoring. I work with Tamar, among other people, and I have been running the Veterans Aging Cohort Study for almost 20 years.

Gore Can you tell me about that? I do not really know anything about it.

Justice Sure, the VA has an electronic medical record system that is national and the Veterans Aging Cohort Study is one of the first large scale cohort studies, observational studies, of people living with and without HIV infection who are veterans. That is nationwide. We have over 50,000 veterans with HIV in the study matched 2:1 for people who do not have HIV. So we have 150,000 people in the study.

Gore So 2 people who do not for 1 that does.

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Justice Yes.

Gore Okay, got it.

Justice So that we can understand to what extent is it that HIV drives the aging phenomenon that people are having, to what extent is it comorbidities, other conditions that people have as they get older and what can we do about it to improve aging for veterans with HIV.

Gore Why was the VA particularly interested in studying prospectively veterans with HIV? I mean, it sounds like a great thing to do, but it is not the first thing that I would have expected the VA to pick up on.

Justice First of all, the study is funded by the National Institutes of Health and has been for more than 20 years because they realized that the VA electronic record was an incredible reservoir for understanding aging, specifically with HIV.

Gore It is one of the oldest electronic medical records in the United States, right, or the world?

Justice It is certainly the oldest national electronic record in the world and we have 20 years of longitudinal data.

Gore It is amazing.

Justice It is really exceptional. What is also very important about it is it is a paperless record. So, some electronic records are not completely electronic. There are parts that are electronic and then parts that are not. Frequently, inpatient records are electronic and other records not so much. But in the VA, it is inpatient and outpatient. It is all pharmacy filled data, so we know about what medications people are taking. It is laboratory data, it is pathology data, it is radiology data, it is everything, which makes it an incredibly rich reservoir for studying outcomes among any kinds of health conditions. HIV has been a priority both with NIH and at the VA for an extended period of time and this was an opportunity to really use it as a chance to study complex chronic disease in aging.

Gore That is amazing. Tamar, how do you interface with this study?

Taddei I actually approached Amy more than 5 years ago now because I was interested in studying chronic liver disease in the VA and since Amy has established the veterans cohort and really understands how to study prospectively these cohorts of patients, she was incredibly generous with her mentorship and taught me how to do this and I applied for a grant and was funded to look at both end-stage liver disease as well as liver cancer in the VA population. She has been essentially my mentor for over 5 years now.

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Gore That is great, and so you are interested in the liver issues in regard to HIV?

Taddei Right.

Gore Diagnostic to HIV.

Taddei Right, the study that I started was diagnostic to HIV. However, it is a cohort that ranges over a period of time and we took every person diagnosed with liver cancer in the VA over a period of time and there are many HIV patients within that cohort. And that is a study that has been going on for about 5 years now.

Justice If I may?

Gore Yes, sure please.

Justice Aging with HIV is an interesting phenomenon even if you are not interested in HIV, because people with HIV have immune dysfunction that is more pronounced than people aging without HIV.

Gore And, is that true even if they are on anti-HIV meds and in good control?

Justice Unfortunately, it is. There are residual effects of the virus. They are much less than when people are not on medication, but there is a constant stimulation of the immune system, which causes depletion of the immune system and inflammation over their lifetime. And how severe that is varies by individuals, but if you are interested in studying a cancer and many forms of organ system disease, the process of understanding it and understanding how to intervene on it is a very important question in biomedical research right now. So people with HIV who are aging with HIV actually provide a very interesting study of that question. Especially when you can compare them to similar people without HIV, and that is one of the reasons why even now we have anti-retroviral therapy and you might think, oh the problems of HIV are solved. They are certainly much better than they were. It is a miracle of modern science.

Gore True.

Justice But these people do not have the same life expectancy as people without HIV. And they are more susceptible to cancer, to cardiovascular disease, to liver disease, to kidney disease, to any number of problems, than people without HIV, and right now, we think one of the major drivers of that phenomenon is this chronic inflammation and immune dysfunction that they experience.

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Gore Obviously in the media, they would have many people, including physicians who are not intermittently involved with HIV care, believe it was not a solved problem, but that the diagnosis of HIV is now a chronic illness and of course these speculations led to a recurrence in unsafe sexual practices among the adverse groups because it does not seem to be a big deal as when some of us were training as physicians when we did not yet know what was causing this crisis. To live with it, you never want to see that happening again, so it is really interesting to hear about these downstream effects that I guess we were all hoping they would not have.

Taddei When you talk about viruses in general, and with HIV we have had a perspective of decades now, but I still think the natural history of HIV is unfolding in front of us and we can actually look at something like hepatitis C, which in many ways a lot of the infectious disease doctors look at liver doctors and chuckle because we struggled for so long to come up with medications, now we actually have very effective medications to treat hepatitis C.

Gore Right.

Taddei But that whole process is one in which the natural history unfolds in front of you, because you are taking a virus which can now be cured in the case of hep C, HIV is a virus that can be suppressed, but there is clearly synergy between these viruses because the patients with HIV tend to have liver fibrosis occurring at a much accelerated rate of their exposure to hepatitis C, so they develop cancer and they develop cancer oftentimes in the absence of cirrhosis, which is different from the sort of non-HIV patient who develops hepatitis C and has a latency period to cirrhosis and then develops their liver cancer. So clearly, there is a difference in that host with HIV and hep C.

Gore Maybe we should take a step back and talk a little bit about who is at risk for liver cancer, you alluded to that a little bit and how this is playing out again in these populations.

Taddei In the West, cirrhosis underlies liver cancer in more than 85% of cases. So anybody with cirrhosis is at risk for liver cancer.

Gore Would I know if I had cirrhosis?

Taddei You would not, and that is a problem. The issue with the liver is that it is a very noble, humble organ that lives right under your right rib cage and does not put off a lot of things that you are completely cognizant of on a daily basis.

Gore I like my liver, I thank it every day.

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Taddei Yes. But the average American does not know where their liver is and does not know what their liver does, and in fact the liver can function normally until about 60% of it is not functional anymore and then somewhere around that 60 to 70% decline in liver function, you will begin to develop symptoms, but by that time, you probably already have cirrhosis. So unless your doctor suspects you may have a liver problem or unless you have abnormal liver enzymes on testing, rarely will you come to the attention of a specialist and some people actually have totally normal liver enzymes and still have cirrhosis, so by the time they get to somebody like me, oftentimes it is too late and then it is a question of managing their cirrhosis. Cirrhosis can be managed for years and people can feel pretty well, especially if the cause of the cirrhosis is something that can be cured like alcoholism, which is probably the number 1 reason for developing cirrhosis

in the US or something like hepatitis C, which now we can cure, and when you can arrest the scarring of the liver even when you have cirrhosis, you will not develop the what we call sequelae or end-stage phenomenon of liver disease, but if you continue to damage the liver, that is when you develop things that can actually lead to liver transplantation or to death and even in the absence of developing those end-stage phenomena, you can develop cancer at any time once you have cirrhosis. In the East or in far Eastern Asia, cirrhosis is not necessarily a precursor to liver cancer. Oftentimes people will develop cancer in the setting of hepatitis B and in places like Africa, you can develop cancer very early from the synergy of hepatitis B, which is often acquired at birth in addition to exposure to aflatoxin, which is just a function of not being able to store grain in cool environments.

Gore Oh wow. Complicated.

Taddei Very.

Justice One of the arguments that we made in the grant that we were able to get from the National Cancer Institute to study liver cancer in people with and without HIV was not only this point about inflammation and how inflammation plays into cancer risk, especially for hepatocellular cancer, but this observation that cirrhosis is not always present in hepatocellular cancer, but frequently is, especially with hepatitis C infection, and to a larger extent, being able to understand what the mechanisms are that connect viral infections like hepatitis C, hepatitis B, HIV, to cirrhosis and liver cancer is a really important question, because if we can intervene on that process even if we cannot always cure the viral infection as in the case of HIV, we may be able to prevent some of the sequelae. That is what we have been focusing on.

Gore Now, in the liver cancers that arise in HIV carrying patients, is the HIV part of liver cancer, does liver cancer have the HIV DNA? Do we know that?

Justice We know that people with HIV have a higher risk of liver cancer even after you adjust for hepatitis C co-infection. They also have a higher risk of cirrhosis given hepatitis C co-infection.

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Justice So, everything is accelerated for them in terms of liver cancer. Why that is, we are still trying to understand. In initial observations, it also appeared as to what I was saying a little bit earlier that people who are HIV co-infected and have hepatitis C do not always have cirrhosis before they develop liver cancer. Which is intriguing, why is that the case? What is happening that causes individuals to go straight to cancer?

Gore I am going to ask you to speculate on that after our break. For right now, we are going to take a short break for medical minute. Please stay tuned to learn more information about liver cancer in the Veterans Aging Cohort Study with Drs. Amy Justice and Tamar Taddei.

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Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore and I am joined tonight by my guests, Drs. Amy Justice and Tamar Taddei, and we are discussing the Veterans Aging Cohort Study and liver cancer. Amy, before the break, you were telling me about this phenomenon of development of liver cancer in HIV positive patients or HIV bearing patients without the development of cirrhosis and you were wondering why that would be.

Justice That was the question that we posed to the NCI.

Gore Did they figure it out yet?

Justice Well, we are working on it. The study that we are conducting together right now is the study that is built off of the Veterans Aging Cohort Study and we use all the data that we have already collected on these 150,000 folks across the country with and without HIV, but we can identify who has had pathological biopsies of their liver that hopefully get both the parenchyma, which is the noncancer tissue and the cancer tissue. And we are lining up 2 pathologists to read those

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specimens in a standardized way independently to make sure that they agree, so that we can compare what the appearance of the tumors are and what the parenchyma appears to be and whether or not there is or is not as much cirrhosis in the HIV infected individuals. Because first of all, it is not even clear that this is a real phenomenon, we want to make sure first of all it is real.

Gore Sure.

Justice And then, try to understand it from a more pathologic perspective with special stains, etc., and Tamar has been essential in helping us set up that study.

Gore Presumably, the pathologists do not know which patients have HIV?

Justice Correct, they are blinded to the HIV.

Gore Do you have any hypothesis or are you just going to see what falls out?

Justice I have lots of hypothesis.

Taddei I think it is important to understand certain things about liver cancer that most people do not really understand at face value, which is what makes the study very important. The first is that only about 50% or less folks who are diagnosed with liver cancer, actually ever get a biopsy, and you know oncologists find this to be completely bizarre.

Gore That is extraordinary.

Taddei Right. How can you tell a person they have cancer without tissue? So liver cancer is the only solid organ malignancy that you can actually render a diagnosis based on imaging alone, and it is because it has a very characteristic appearance and so if you have the right host a person with cirrhosis and a cancer that enhances appropriately, you can call it liver cancer and this is done all over the US and the world all the time, and the problem is that we do not have enough tissue as a result of that.

Gore To study you mean?

Taddei Exactly, and so in HIV patients and in some patients who have early cirrhosis that may not look like cirrhosis on imaging, when we are not sure if they have an underlying diagnosis of cirrhosis, we will do a biopsy. Because we really want to confirm that it is liver cancer. Likewise, if perhaps the patient has cirrhosis, but the cancer does not enhance exactly as we would expect on imaging, we would do a biopsy, so we do have guidelines for when we should biopsy these

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people and yet we still have a dearth of tissue out there to examine under the microscope. So this study really takes a group of biopsies and in a blinded fashion we are able to characterize the morphology of these liver cancers and look at the background tissue when there is background tissue. We are getting a bevy of specimens that are either resection specimens when we have a lot of tissue and we can really examine the background, the interface of the background with the tumor and the tumor itself and we also have biopsy specimens which are more challenging, but we have really tried to cast as wide a net as possible so we can see as many different types of tumors as we can and in what milieu they arise. So, we are looking at the tumor interface with the background as well as the tumor itself and liver cancer also morphologically takes on many different patterns so much so that many pathologists kind of wonder if we're lumping a bunch of cancers together. So, that is another question, does the cancer morphologically look different in the HIV positive patient versus the

non-HIV patient? And some people say, what can morphology really tell you? But it really can tell you a lot.

Gore I do not question that because I find that in my field the more we understand about the genetics of certain leukemias, I realized that at least in certain kinds, the morphology really integrates how it looks, has integrated the genetic information which makes sense. The pathologists can see that this is a worse something which is borne outside the genetics. On the other hand, it is really nice for us to have the genetics.

Taddei Right.

Justice So speaking of genetics, the VA is also conducting a very large study called the Million Veteran Program where they have enrolled now over half a million veterans and they are hoping to get to a million who have given permission for full access to their electronic medical record data and given a DNA specimen. And we are hoping down the road to be able to link our study with that study so that we would both have the genetics of the individual and the genetics of the tumor.

Gore Right. Because the million vet thing is for their germline.

Justice Yes, their germ line.

Gore Their inherited DNA right?

Justice Correct.

Gore Are you actually going to be able to get DNA from these pathology specimens from the liver cancers to study?

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Justice Down the road, we are hoping to do that.

Gore You require more money probably?

Justice Well, it will require two things. It will require more money and more permissions. We initially only have asked for permission to study this tissue.

Gore Morphologically, the way they look.

Justice Right. And the VA wants to be very, very careful to protect patients.

Gore Of course.

Justice In terms of their privacy, so we have to walk before we run. Our first step is to get the specimens to describe the morphology and to demonstrate that there is an adequate scientific question to justify further exploration and then go back to the IRB and get permission, we hope, eventually to do DNA studies. Right now, we do not have that permission.

Gore The IRB is the ethics board.

Justice Correct.

Gore How many patients are we talking about? I mean how many cases of liver cancer are you studying?

Justice We currently have over 40 and our goal is to get 300.

Gore I see. So this is a not an unimaginable task.

Justice No. But because this is nested within the larger Veterans Aging Cohort Study, all the issues that Tamar was talking about, who gets biopsies and who does not get biopsies, we will be able to see who we got the biopsies on and whether or not the people who did not get biopsies were much more likely to have documented cirrhosis for example and adjust for that in the analysis, so that we can have a less biased view even interpreting the pathologic specimens that we get.

Gore And these specimens are all coming from West Haven, or are they coming from VAs all over the United States? Are there other VAs elsewhere?

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Justice Yes, there are. We do not include samples from Guam, or somewhere like that, but actually Puerto Rico is one of the sites.

Gore Gotcha. Even to get 300 samples identified and shipped from all over is really a major organizational task.

Justice Yes, it is.

Gore And did you find that most of the centers were happy to cooperate?

Taddei Most of the centers are happy to cooperate. If you think about the nature of this type of research you are asking a pathologist at a center far away to pull blocks of tissue to identify the most representative block to cut slides, if they want to cut them or to send the block, it is work. So we have tried to make it as easy as possible for the pathologist, we send them a packet, we send them the specimens that we have identified. There is not a lot of leg work that they have to do, but there is still the leg work involved in pulling the cases, examining them and sending the block, etc. So, yes, we are really relying on the goodwill of folks at other VAs, but I have to say that the VA is a phenomenal place to do research where people really are aligned behind the singular mission which is to help care for the veterans and to improve their health over time and research is a big part of that, and this type of research usually leads to very collaborative groups, so that pathologists are saying wow this is a neat study, can we come to your yearly meeting, can we work with you on the abstracts, so I think the whole nature of this type of research lends itself to developing collaborative networks and research has to be collaborative these days.

Gore Yeah.

Taddei No one person can have the expertise to answer all of these questions. So yes, they are very helpful and very interested and we have a phenomenal team and in large part due to Amy's already phenomenal organization, but just the ability to be positive and as she says like water on a rock.

Gore Now most of the veterans that are being studied are they mostly Vietnam veterans or we going back even farther?

Justice We will include anyone who is in the study who has hepatocellular cancer and we have some 80-year-olds in the study and 90-year-olds, so some of those are not Vietnam veterans.

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Gore I see, and I guess the causes of cirrhosis and cancer varies like in any other population, probably a fair amount of alcoholism I am guessing.

Justice There is. The VA is very careful about collecting data on alcohol consumption, so we actually have very good measures of alcohol consumptions. It is one of the reasons that NIAAA, which is the alcohol institute, has been one of my major funders over the year. We have spent a lot of time studying alcohol and actually other substances as well. We probably have a better handle on that exposure than many other cohort studies might have. Part of what is exciting about this study from my perspective as an epidemiologist is this is really one of the first studies to capitalize on the electronic medical record as a way of building a cohort. If you think about the famous cohorts before, Framingham, for example, they cost the taxpayer an incredible amount of money, because you had to go out and recruit those patients, do physical exams.

Gore Follow them, all those years.

Amy Support all the stuff, get the lab tests, follow them. If instead we can use our networks of hospitals and clinics to do efficient observational work, we can save the taxpayer a great deal of money and have clinically relevant observations that can directly be fed back in terms of clinical management and that is part of the model that the VA has been trying to build over the last 20 years and I think pretty effectively.

Gore Did they build the electrotonic medical record in the VA System to be particularly research friendly?

Taddei One of the major benefits the VA has is that they implemented the paperless medical record 20 years ago.

Gore Right.

Taddei So they have been able to learn over time how to make it more user friendly, both for clinical management and for research. Initially it was called the 'decentralized' because while every VA in the country had to adopt it, how they named the data field was somewhat up to them.

Gore That sounds chaotic.

Taddei Yes. Now, over the years, that has become much more standardized. We have very standardized information about medications, about laboratories and standard note fields, pharmacy data, etc. So that we can now analyze this data nationwide very effectively and it is really the only system people talk about. Kaiser, while it is a national system, their data is

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regional, not national, so Kaiser Northern California, Kaiser Southern California, etc. The VA has a national HER, we pull data nationally on these people, so someone seen in Florida half the year and Connecticut the other half of the year, we have both sets of data to be able to look at, which is helpful for patient care certainly, I can say as a primary care doctor but also extremely helpful for research.

Gore What percentage of the VA population now is female?

Justice About 25% of returning veterans are female in this age group.

Taddei In this age group, it depends on which age group you are talking about.

Gore So you still have that issue to deal with that it is not yet fully representative.

Amy Absolutely, but in the Veterans Aging Cohort Study which is focused on HIV, we have as many women in that study as the women's study focused on women with HIV. Because it is such a big sample, so the percentage is small, but the absolute numbers of women actually is not small. We have over 1000 women in the study.

Dr. Amy Justice is Professor of Medicine and General Medicine and of Public Health in Health Policy at the Yale School of Public Health and Dr. Tamar Taddei is an Associate Professor of Medicine in Digestive Diseases 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. You are on WNPR, Connecticut's public media source for news and ideas.