

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



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The Link Between HIV and Cancer

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar and Steven Gore. 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. This week it is a conversation about the link between HIV and cancer with Dr. Robert Dubrow and Dr. Amy Justice. Dr. Dubrow is Professor of Epidemiology in Chronic Diseases at Yale School of Medicine and Dr. Justice is Professor of Medicine and of Public Health and Section Chief of General Internal Medicine for the VA Connecticut Healthcare System. Here is Dr. Anees Chagpar.

Chagpar Let's start by talking a little bit about why this is an issue at all. I mean, we heard a lot in the 80s especially about HIV, but now it seems that we are talking more about other diseases in a population where, oh by the way, is living with HIV. Do you want to put that into a larger context for us?

Justice The good news is that we have therapy that is very effective at suppressing the HIV virus so that people are no longer rapidly progressing to death from HIV which has been a wonderful thing I can say as a physician to have watched over my career. However, that means that with almost every year people with HIV in this country are aging by a year, so a disease that was traditionally something we saw in young adults to middle-aged adults is rapidly becoming a condition we see in middle aged and older adults, many of whom have been living with the virus now for decades and that has many implications in terms of multi-morbidity, not only cancers but other conditions as well associated with aging that people with HIV appear to be at greater risk for including cardiovascular disease, for example. They often have hepatitis C co-infection as well which means that their liver may be compromised and they may progress to conditions that we will probably talk about later and that means that they also have multiple conditions and multiple medications or polypharmacy, so in many ways many people who are aging with HIV say they feel much older than their stated age because of all these other things going on and that is something that we as a society need to understand how to manage in order to optimize outcomes for those individuals and to not forget about their other issues, so it is not so much, oh by the way they have HIV. HIV does still influence what is happening for them, not nearly as dramatically as in the 80s thank God but it is still something that we have to be very cognizant of and pay attention to and it is certainly extremely important to get everyone's virus suppressed so that they have an undetectable viral load and that needs to happen right away.

Chagpar Maybe we can talk a little bit as well about the fact that it is great news that people with HIV are living longer, but do they have an increased risk of developing cancer over the general population who are also getting older? Or is it that we are simply talking about cancer in this population because now they are living longer to get cancer?

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Dubrow That is a great question. Let's go back to the history of HIV. In the beginning the way HIV came to light was through seeing both what we call opportunistic infections, unexplained but also a certain type of cancer called Kaposi's sarcoma which is very rare in the general population but it turned out was being very common in HIV infected people, so ultimately, as HIV began to be understood, the CDC identified three what were called aids to finding cancers, so one was Kaposi's sarcoma, the second was non-Hodgkin's lymphoma and the third which was added later actually was cervical cancer, and those were considered AIDS defining, so if a person was HIV infected and has one of those cancers, then they by definition have AIDS. After 1996 or so, when this powerful anti-retroviral therapy treatment became available, the situation with cancer started changing, so before 1996, really the majority of cancer seen in HIV infected persons were the AIDS-defining cancers at much higher levels than in the general population; here we are talking about relative rates of Kaposi's sarcoma, for example, of a 1000 or more.

Chagpar Wow.

Dubrow For non-Hodgkin's lymphoma, in the order of 20-30, but the situation shifted with anti-retroviral therapy. The rates of the AIDS defining cancers dramatically decreased, although they remained still substantially higher than in the general population, but what started being uncovered were actually elevated rates of other types of cancers which were called non-AIDS defining cancers and let me tell you what some of the main ones are. First we have human papilloma virus associated cancers with cervical cancers being one of those, but in addition, we have anal cancers in which there is about a 30-fold elevated risk, Hodgkin's lymphoma with about a 10-fold increased risk and Hodgkin's lymphoma is not HPV related. Some of those are related to Epstein-Barr virus and the other HPV related cancers that are a portion of the oral cavity and pharynx cancers which are elevated as well as other genital cancers like penis cancer and vaginal cancer, those are elevated. Then we have Epstein-Barr virus related cancers in addition to Hodgkin's lymphoma, a certain portion of non-Hodgkin's lymphomas are related to Epstein-Barr virus and as we have already said, those are elevated. Then finally, we have the hepatitis C virus and hepatitis B virus which are major causes of liver cancer and liver cancer incidence rates are also elevated three to five fold, so there is a theme here that it is viral related cancers that seem to be ones that are highly elevated in HIV infected persons. There is one exception that I should mention because it is very important and that is lung cancer which is about two to three fold elevated among HIV infected persons and that is partly due to the fact that there is a high prevalence of smoking in this population, but some of the studies that we and others have done have found that there is an independent effect of HIV infection as well and that is not well understood; the reason for that is not yet well understood because as far as we know, lung cancer is not a virus related cancer.

Chagpar So why is it that people with HIV are more prone to viral related cancers, what is the mechanism behind that?

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- Justice Like multi-morbidity, it is not one mechanism but several. Some of the risk factors for HIV virus are also associated with risk factors for cancer, so substance use, risky sexual behaviors also puts you at risk for not only co-infection with some of the other viruses that Dr. Dubrow was talking about, but also can increase your risk of cancer because of underlying inflammation, because of other injuries that are caused by those substances. Alcohol is notorious for causing progression of liver disease, for example, and liver cirrhosis is strongly associated with the risk of liver cancer. We know the story with smoking and lung cancer. One of the things that I think is intriguing thinking about HIV, I am a general internist, I am not an oncologist, but I am very interested in this because I think that HIV can offer us insights into the etiology of these conditions associated with aging for those without HIV as well and that it shows a different angle on what is happening with these conditions, so Rob has written a lot about inflammation and its association with cancer and some of the reviews we have written together and that certainly is an important piece, the chronic inflammation of the virus, there are some people who speculate that there may be direct effects of viral proteins that also cause an acceleration of cancer; there is also a question quite honestly of whether or not folks with HIV are less likely to get their cancers diagnosed in a timely fashion and that is something we are going to begin to try to study more generally.
- Dubrow I think there is one other factor that we should mention, the HIV virus attacks cells called CD4 cells, CD4T lymphocytes to be more specific, which are critical cells in the immune system and one of the parameters that is closely monitored in people with HIV is this CD4 count, so roughly speaking, a CD4 count of greater than 500 is considered to be good. Once you get below 200, that is actually considered as defining, so that is bad and we have done a fair amount of work looking at the relationship between CD4 count and cancer incidence among HIV infected persons and for many of these viral associated cancer types, we do find an inverse relationship, so the lower the CD4 count, the higher the incidence of these cancers, so that is another important mechanism.
- Justice So it's behaviors, yes, but even after you adjust for behaviors, it is also immune function as measured by CD4 and even after you adjust for immune function, it is also viral burden. Rob and I co-mentored an individual who just finished her PhD thesis looking at the viral burden and whether or not that was an independent predictor of these cancers and it was, so it's all of the above and not any one.
- Chagpar I guess it can make sense when the lay person is kind of thinking about, what is the etiology, how does this all work, that perhaps you cannot mount an immune response against a virus and so then the virus, whether it is HPV or another, can predispose to various cancers, it is interesting that viral load also is a correlative factor and whether that is just related to how bad the disease is, any speculation on why that is?
- Justice Well again, if in fact there are direct effects of viral proteins, viral load would make sense separate from its effect on the immune system.

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Chagpar So when you say the effect of viral protein, what do you mean?

Justice In terms of what mechanism would the proteins have, proteins can frequently mimic other proteins and have effects that are not “intended” and that could include suppressing or accentuating certain activities in terms of the cell that might lead to greater reproductivity with less careful sex, these sorts of things lead to cancer more generally. That is not well understood and the research on that is only beginning, but I think it is an intriguing possibility given the strong association not only with HIV virus but with co-infection with other viruses as well..

Dubrow Also, if I could explain that a little bit more. The viral load is kind of a rough proxy for inflammation and paradoxically, even though there is immune deficiency you see a paradoxical, as Amy was already talking about, chronic inflammation and that is due to the fact that because first of all you have the HIV infection which is related to inflammation itself, but also because of the immune deficiency, we have a lot of other infections that pop up, Cytomegalovirus, as an example that causes chronic systemic inflammation and again inflammation is well known to be related to cancer incidence, so I think that is another mechanism.

Justice There is another interesting piece to the inflammation story which is that immediately after viral infection people’s lymphatic system along their GI tract is largely destroyed. Those are not really recreated even in people who have a very good response to therapy. That means that the sentinel activities of that lymphatic system to prevent toxins from crossing the GI tract and getting into the blood stream is reduced. Those toxins hit the liver, the liver cannot manage as many of them, so that also feeds into this chronic inflammatory process which may well stimulate many of these conditions.

Chagpar We are going to pick up on that conversation but first we need to take a break for a medical minute. Please stay tuned to learn more information about HIV and cancer with my guests, Dr. Dubrow and Dr. Justice.

Medical Minute

There are over 13 million cancer survivors in the United States and over 100,000 here in Connecticut. Completing treatment is an exciting milestone but cancer and its treatment can be a life changing experience. Following treatment, cancer survivors can face several long-term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers to help keep cancer survivors focused on healthy living. The Survivorship Clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to maximize their health, quality of life and longevity. This has been a medical minute brought to you as a public service by Yale Cancer Center 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.

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Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guests Dr. Robert Dubrow and Dr. Amy Justice. We are talking about the relationship between HIV and cancer and before the break, we spent a lot of time talking about why people with HIV may be at higher risk of developing cancers, mainly viral related cancers, but really a whole lot of other cancers as well, people with HIV are living longer, but also have a number of risk factors that increase their risk of developing other cancers, so I want to come back to this idea of how can we do better for HIV infected populations in terms of preventing and treating cancers? Amy I want to start with you because you made a very important point that I do not think we adequately discussed before the break, which was access to care and whether patients with HIV feel welcome in environments and have appropriate access to care because without that access it is really difficult to have any real impact in terms of prevention and treatment.

Justice There are a number of things that you need to think about when you are talking about access. If you are talking about access for HIV treatment, people in the United States have generally good access for HIV treatment with a few exceptions. People can get anti-retroviral therapy fairly readily, so that is very important, if you do not treat HIV, people are not going to live long enough to have to worry about the cancers, quite frankly, but once they get access for their anti-retroviral therapy, you need to think about access for general healthcare management because many of these clinics have been very focused on treating HIV alone and they have done a great job of doing that, but they are staffed by people who are extremely focused on HIV and may not appreciate all the other issues that come with aging and there are many different models for how that might be addressed. The passage of the Affordable Care Act may very much help this issue because it now means that they can pay for some of those treatments; previously that was a big issue because the funding mechanism for paying for HIV treatment did not cover payment for other methods. I have the benefit of working in the VA system where people could get treatment easily for these other conditions, but until recently that was not necessarily true outside the VA, so I am very glad for that development. Nevertheless, the coordination is going to be challenging between the infectious disease doctors who tend to do HIV treatment and the whole group of physicians that are needed and other providers that are needed to care for cancer, appropriate screening and the other conditions we were talking about, and of course disparities do develop along the lines that you might expect; people who have insurance may be more readily able to get that kind of care, people who understand how to use the healthcare system may be better able to use this system appropriately to get the care they need, so coordination of care is going to be very important.

Chagpar And speaking of stigma, we have had people on this show before who have talked about LGBT issues, which certainly remain an issue and something that I think we need to keep top of mind in terms of making sure that our healthcare system really does focus on the entire population and not just those that are straight, so I would like to get now to the issue of prevention and Robert, before the break, you talked about many of the behaviors that predispose both to HIV as well as to other cancers, smoking, alcohol, etc. Should patients who are HIV infected take particular caution to reduce those risks?

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- Dubrow Yes, let me backtrack and give a general overview of the way I see cancer prevention in this population. I think there are three important aspects, and one is early and sustained anti-retroviral treatment and because, as I talked about, the lower the CD4 count goes, the higher the risk for cancer, so if people start being treated early when their CD4 counts are still relatively high, then that should be good with regard to cancer. The second pillar of prevention would be what you were just referring to, reduction in the prevalence of cancer risk factors, and I will get back to that in a second, and then I think the third pillar is certain aspects of cancer screening. Let me just expand a bit on each of those. First, the early sustained anti-retroviral therapy, and in spite of the access, this is still an issue because HIV infection, until the later stages in AIDS, is pretty much asymptomatic, so people could be walking around with HIV infection for years and not know it if they do not get tested and so there has been a big push by the CDC to try to expand testing because now we can do something very positive for people with HIV, which is to start them on anti-retroviral therapy. It is estimated that about 20% of people who are HIV infected in the United States do not know that they are infected, so that is important. With regards to reduction in risk factors, I mentioned the prevalence of smoking is about 50% in HIV infected compared to 20% in the general adult population so that is a hugely elevated prevalence of smoking. That would warrant that be on every HIV physicians mind in terms of recommending smoking cessation, actually doing smoking cessation therapy which could be a combination of behavior and pharmacologic approaches, so that should be automatic. Smoking not only causes cancer, as you know, it causes a lot of other morbidities, same with alcohol, we know that there is higher prevalence of alcohol consumption. Alcohol causing oral cavity and pharynx cancers, esophageal cancers, other types of cancers, so conscious interventions to try to control alcohol consumption is also important.
- Justice If I can just jump in there.
- Dubrow Yeah sure.
- Justice We have done a lot of work on alcohol and there is a lot of evidence to show that for the same unit exposure to alcohol, people with HIV are much more susceptible to its effects, so it takes fewer numbers of drinks to begin to feel intoxicated. It takes fewer alcohol exposures to have associations with mortality and morbidity and likely the same will be true for these cancers, the cirrhotic events and the liver cancer that we talked about before and the other thing is that we have shown that any amount of alcohol interferes with adherence to antiretroviral therapy.
- Chagpar So it is a double whammy.
- Justice You can think about it like, you come home at night, you take a drink, you might be a little less likely to remember to take your meds that night, so even if it is not directly physiologically harmful, it gets in the way of the most important thing which is taking your anti-retrovirals.

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- Chagpar Yeah.
- Dubrow If I could just go back, you had mentioned vaccination. There is a vaccine against hepatitis B virus which causes liver cancer, so that is routinely recommended especially for HIV infected persons. There is also a vaccine against human papilloma virus and that is a little more complicated because typically we want to be vaccinated before we have been exposed to the virus, so usually when someone reaches the point where they are HIV infected, many of those people have also already been exposed to human papilloma virus infection; however, there are some encouraging studies, and this still needs more research, but there are some encouraging studies that indicate that perhaps the vaccine could be of benefit in this population even if they have been previously exposed to the virus. And let us turn to treatment of hepatitis C virus infection, which I will let Amy talk about.
- Justice I think this is very important. Almost half the people with HIV, have hepatitis C co-infection and we know that hepatitis C co-infection progresses more rapidly in people who are HIV co-infected even after you treat them although treatment for HIV slows the progression of hepatitis C, so that is the good thing, and it seems only sensible that we want to get co-infected individuals into treatment for hepatitis C since we can cure hepatitis C now with great reliability, so that is one less comorbidity they have to live with and that is one less set of viral burden and inflammation that they have to go into older age with, so I think treatment of hepatitis C is going to be incredibly important in terms of preventing some of these downstream problems for people with HIV.
- Chagpar Talk a little bit more about the treatment of hepatitis C because as you said this is something that now we can treat. Talk about that treatment and particularly about the cost and whether that is covered by insurance for a population who quite frankly may not always have the best insurance.
- Justice The treatment of hepatitis C is recommended and many insurers are covering hepatitis C treatment. It is quite expensive. People have estimated that the cost of achieving viral suppression is about 100,000 dollars for an individual if you had to pay out of pocket. The VA pays for it. Many major insurers pay for it. The federal government pays for it for the people who qualify. The Affordable Care Act individuals are covered and in fact interestingly even though it is a very expensive thing to treat, I am hearing from my colleagues who are setting up clinics to do hepatitis C treatment that actually the reimbursements that are offered by the insurance companies are fairly good, so it is not a money loser for healthcare systems which means the systems will hopefully be more likely to set up good clinics to do the treatment. General internists are beginning to treat hepatitis C because the medications are much less toxic, much more easily tolerated. The requirements for treating individuals are much less difficult and they are even expanding treatment to people who have substance use issues which I think is also very exciting.
- Chagpar That is going to be a huge help in terms of reducing the number of cancers that we find in patients who have HIV, if we can treat co-infections with hepatitis, if we can potentially prevent some cancers either due to HPV or smoking or alcohol related cancers. Let us talk a little bit about screening. One of the greatest things that I think we have done in cancer over the last several

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decades is improve early detection and it would seem to me that in a population at high risk this is something that is important. Are the guidelines any different for HIV infected individuals as for the rest of the population and if not, should they be?

Dubrow Good question. First, let's look at the cancer types where there are firm guidelines, there is colorectal cancer and it is the same for colorectal cancer. There is Pap screening for cervical cancer. Those screening recommendations are somewhat more intensive for HIV infected women which has been very successful, so the incidence rate of cervical cancer in HIV infected women is barely higher than it is in the general population now, so that has been very successful. As you know, prostate cancer screening is controversial, it is currently not recommended by the US Preventive Services Task Force, so let us skip that one, and breast cancer screening would be the same and there is no special recommendation for breast cancer, but let me mention three other cancer types for which there is currently no recommendations that are important in this population, anal cancer, liver cancer, which we talked about already, and lung cancer. And let me amend that, there is now a recommendation for the general population for lung cancer, so let me turn to that one first because there are issues with regard to HIV infected persons which are that there are good reasons to suspect that you might have many more false positives with CT scan screening and false positives are bad and so there needs to be more research in that area. Anal cancer screening is probably a lot like cervical cancer versus HPV but it still has not been proven that it is a benefit and there are active trials right now trying to prove that.

Dr. Robert Dubrow is Professor of Epidemiology and Chronic Disease at Yale School of Medicine and Dr. Amy Justice is Professor of Medicine and of Public Health and Section Chief of General Internal Medicine for the VA Connecticut Healthcare System. 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, archived programs are available in both audio and written format at yalecancercenter.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.