

Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is a medical oncologist specializing in pain and palliative care and he also serves as Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening we are joined by Dr. Kevin Kelly. Dr. Kelly is co-Director of the Yale Cancer Center Prostate and Urologic Cancers Program, and he is Associate Professor of Medical Oncology at Yale Cancer Center. He is here this evening to speak with Ed and Ken about new treatment options for advanced prostate cancer.

- Kelly Prostate cancer is a very common cancer and the greatest risk factor for prostate cancer is age. As you age you have a higher risk of developing prostate cancer. By the age of 75-80, 75% of men will develop prostate cancer, but this does not mean that younger men cannot have prostate cancer. Patients whose family has a history of prostate cancer are at an increased risk for developing prostate cancer, and these patients need to be screened for prostate cancer earlier, starting even at the age of 40 in some cases. African Americans also have a higher incidence of prostate cancer, in particular, if they have a family history, you have to be particularly cautious to be screened for prostate cancer, because they are at a very risk for developing prostate cancer even at an early age.
- Miller Kevin, for women there is a lot of talk about the BRCA gene, the gene that predisposes women to breast cancer. Have we identified a similar gene yet in prostate cancer, or are we getting close?
- Kelly We are learning more and more about the genetic makeup of prostate cancer, however, the majority of what we see for prostate cancer is what we call sporadic, and most of the genes that we find for prostate cancer count for around 10% of prostate cancer. What is interesting is that in families that have BRC mutations, it has been found that the male offspring are 50% at risk of developing prostate cancer. This is a very high-risk group of patients and there are multiple other new genes that we are discovering right now that are being linked to the development of prostate cancer.
- Chu Other than age, which clearly is a very important risk factor, are there any other risk factors that one needs to think about?
- Kelly That is the number one risk factor right now. That is the one that is established. Others are still being validated on how they actually develop prostate cancer.
- Chu What about this issue of benign prostatic disease, which unfortunately, I think all of us sitting here at the table this evening, are at an increased risk for? Is there

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any truth to the concern that if you have benign prostate disease that you are going to be at increased risk for developing prostate cancer?

- Kelly No, there is no definitive evidence that if you have BPH it leads to prostate cancer. The problem is that the symptoms of prostate cancer and BPH can be very similar, such as difficulties urinating, so these symptoms need to be evaluated by your urologist and followed. It is important to get a baseline PSA in people who have prostatic symptoms either from infection of the prostate, BPH, or have a family history of prostate cancer. Because what we are finding out is that what is probably more important than the absolute value of PSA is the PSA history or what happens over time with PSA.
- Miller What I am thinking about, and our listeners, is there any way to reduce the risk of developing this common disease?
- Kelly There is a lot of work going on. There are multiple large clinical trials looking at different vitamins, such as vitamin E, and Selenium to see if this actually decreases the risk of prostate cancer. Today, there are no vitamins or anything else that has been shown to decrease the risk. There is a lot of epidemiology data that looks at different proportions of prostate cancer in populations around the world. For instance, in Asia, there is a very low risk of prostate cancer, but if you bring these individuals from Asia to say California, within one generation they develop the same risk as the American population. This suggests there is an environmental factor, whether it is dietary or other environmental factors, that effects the progression in the growth of prostate cancer.
- Miller In the coming years we are going to hear a lot more information about what causes prostate cancer to develop and some preventative methods.
- Kelly There are premalignant lesions for prostate cancer called PIN, or pre-interstitial epithelial neoplasia, and if you have that, there are drugs out there that have actually been shown in clinical trials to delay the onset of prostate cancer.
- Chu Are there any men who are at a particularly increased risk for developing this PIN, as you call it?
- Kelly It is still age, but we are still trying to understand the molecular mechanisms of why PIN develops, but we know that the majority of patients with PIN will eventually develop prostate cancer. It is a premalignant lesion that needs to be addressed and followed closely by a urologist.
- Chu And you were saying that there may be some drugs that can help prevent that from progressing?

- Kelly Yes, we know there are drugs and we know that in prostate cancer the main driver of the development of a prostate cancer is your male hormone, testosterone. There are drugs that actually decrease low levels of testosterone in your prostate, such as drugs called finasteride, which may actually help prevent the onset of prostate cancer.
- Miller The other good thing about it is the lower doses of Propecia.
- Kelly That is correct. It grows hair.
- Miller So there could be two advantages for you. I want to ask you about screening. In general, what would you recommend for men in terms of screening, and at what age? And if someone needs even closer follow-up, how would their surveillance approach be different?
- Kelly Recently there has been a lot of controversy in the press about the use of PSA screening, but currently the recommendations from the American Cancer Society and the American Urological Society, are that men age 50 should have a digital rectal exam and a PSA done yearly. Patients at high risk, such as African Americans and patients with a family history, should start at age 40. There are other task forces that have looked at this and their recommendations are changing a little. It is still a very controversial area because of the risk and benefits of developing prostate cancer, and risk and benefits of treatment.
- Chu What is the incidence of prostate cancer in some of the other ethnic groups such as Hispanics, Asian Americans, etc.?
- Kelly It is not that different than the white population, again, it really relates to the environment therein. Further studies show that in industrial nations that actually have more fat per capita, the rate of prostate cancer is much higher. We live in a very varied society here, and diets and other things change greatly.
- Miller I had a question from a neighbor a number of weeks ago, and he essentially asked if he is having his PSA tested every year, why does he need to have a digital rectal exam?
- Kelly That is a great question, and one that I get all the time. Nobody likes the digital rectal exam, but you do get added information from that. PSA is just one component of it. The PSA is secreted by normal cells; it is created by prostate cancer cells. So, when you do a digital rectal exam, you are looking for abnormalities in the prostate, whether it is BPH or nodules there. There are times when PSA may not reflect the presence of cancer. We know that with prostate cancer, as the cancer becomes more aggressive, they secrete less PSA. So, a very aggressive prostate cancer can have a very low level of PSA in the blood.

That shows the importance of doing a digital rectal exam and doing serial PSAs over time to see what the PSA history is, because small change in the PSA may be significant in the individual.

Chu Those are really important messages that you are giving us Kevin, because I think the common misconception is that even if you have a mildly elevated PSA, that means it is cancer and it is bad news, but in fact, as you just pointed out, there may be benign causes that can cause the PSA to be elevated.

Kelly That is correct, I mean the PSA for a 45-year-old should not be the same as an 80-year-old. The quantity of PSA will be different, so we can accept somebody's PSA at the normal range up to 4, in somebody 75-80, their normal may be 5 to 6, while in somebody who is 45, I would expect the PSA to be between 1 and 2; usually less than 1.

Miller I want to dive into this issue of controversy. What is the controversy about PSA? What is the trouble there?

Kelly Well, the controversy is if screening is decreasing the number of deaths from prostate cancer and the morbidity from the treatment, and if the risk benefit ratio of treatment is worth it all. Again, if you look at the studies that have been done out there, is that when you do PSA screening and you find prostate cancer, you are addressed with a question whether to treat it or not. If I treat it, what type of treatments do you do and what are the risk factors of those treatments? Some studies that look at the satisfaction of patients who have treatment show that they have been dissatisfied with the treatment because of urinary incontinency, impotency, which are the most common side effects from the treatment of prostate cancer. However, the real question is if we are treating the right people that need to be treated. Are we treating too many people that do not need to be treated? It does not mean that if we treat patients with aggressive tumors, that we will have an impact on the overall outcome of these patients and their overall quality of life. So I think the way you ask the questions, and what your end points are, are very important in the studies.

Miller You are listening to Yale Cancer Center Answers here with Dr. Kevin Kelly who is Associate Professor of Medical Oncology. We are talking about the latest information about prostate cancer treatment.

Medical Minute

Here in Connecticut the American Cancer Society estimates that almost 1000 people will be diagnosed with colorectal cancer every month. The good news is that when detected early colorectal cancer is easily treated and highly curable. That means that if you are over the age 50, you should have regular colonoscopies to screen for this disease. In the case of patients that develop

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colorectal cancer, there are more options than ever before thanks to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. The patients enrolled in these trials are given access to medicines not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at www.yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am joined by my co-host, Dr. Ed Chu and our guest today is Dr. Kevin Kelly who is an expert on prostate cancer. We are talking about the latest options available for men with prostate cancer. Kevin, can you tell us a little bit about the stages of prostate cancer and how that affects your approach?

Kelly There are multiple stages of prostate cancer and when prostate cancer is localized to the prostate gland itself without any distant spread, which means involvement of lymph nodes or bones, you have what we call locally advanced prostate cancer. When the cancer has grown outside of what we call the prostate capsule, but has not spread anywhere, then you have distant metastasis from prostate cancer. Patients with it totally localized to the prostate are very amenable to curable approaches such as radiation and surgery, and some of those might be appropriate for just observing. Patients with more advanced disease typically do have problems with prostate cancer and need active treatment for it, but prostate cancer is also what we call a hormonal treated tumor, so not only do we have to know the extent of cancer, but whether or not they still respond to the male hormone testosterone. We typically classify these not only on the extent of the cancer, but whether or not it is what we call castrate or non-castrate disease states.

Chu Kevin, when a patient is diagnosed with prostate cancer, what would be the typical approach to deal with this individual in terms of what the best treatment options are, and who is going to be overseeing the care of that patient?

Kelly There are many qualified people that can quarterback the care, from the internist, to the radiation oncologist, or urologist, even the medical oncologist. The things that are needed when someone is diagnosed are to understand what the initial PSA is, what is the PSA history, what is the Gleason score, the grade of the tumor, and the clinical stage of the disease. Those are the 3 main characteristics you need. With that, we have what we call risk models, where we can tell if a patient is what we call low risk, intermediate risk, or high risk, of the cancer escaping from the prostate gland. That can help guide some of the treatment decisions at that point. We use a nomogram to actually plug these numbers in and they can compare it to thousands of patients who have either had radical prostatectomy before, or a type of radiation therapy, and tell you how well you would do with each treatment

modality. It would also tell you, if you go to surgery, what your chances are of the cancer being confined to the prostate, or the chances of it being involved in the lymph nodes at surgery also. We work very closely in what we call a multidisciplinary team, which means that as patients come through, we assess the risks and we discuss them in our tumor boards so that we get input from the radiation oncologist, surgical oncologist, urologist, and other medical oncologists or people who are at the conference. This allows us to get a better-rounded opinion of the best treatment for our patients.

Miller I want to ask you about a different population, men who appear to have cancer, it is not metastatic, it has not gone elsewhere in the body, but it is regionally advanced. There is a talk about using preoperative therapy, can you tell us about that?

Kelly There is a lot of work that has been done with preoperative therapy. The studies right now have shown that if we use what we call hormone therapy, drugs such as Leuprolide or goserelin acetate which lower the male hormone testosterone, before with radiotherapy and for a prolonged period after radiotherapy, it has been shown to improve survival. The more aggressive approach is now trying to introduce chemotherapy before surgery, after surgery, or after radiotherapy. There are randomized trials ongoing right now like the ones that have been performed in breast cancer and also colon cancer, but it will be a few years before we know what the role of chemotherapy is in this aggressive type of cancer.

Chu What about patients who have more advanced disease and the prostate cancer has spread beyond the local confines and it has gone to other areas throughout the body?

Kelly Typically what we use for that is hormonal therapy, or lowering the male hormone testosterone. Also, for very aggressive cases, there are clinical trials looking at chemotherapy and hormonal therapy in those populations. We do have several trials looking at novel approaches to give further advantage to hormonal therapy, for instance, we are looking at a trial here for hormonal therapy plus another drug to actually starve the blood vessels from the new tumors.

Chu Can you explain to us, and our listeners out there, what hormonal therapy really means? Are you giving hormones to the patients with prostate cancer or are you trying to reduce the hormone?

Kelly That is a great question, because this is a question we always get. Testosterone is made by two principle sources, your testicles and your adrenal glands. Historically, one way to lower the male hormone testosterone, which is the treatment for prostate cancer, was to remove the testicles. However,

there are now medications we can give to a patient that sends a sort of signal to the brain, and from the brain to the testicles, which tells them to stop secreting testosterone. These drugs are called hormonal therapy, typically, and the most common ones are drugs like Leuprolide or goserelin acetate.

Miller I have a question. When you wake up in the morning and are on your way to work, what projects are you really excited about right now? I know you are doing a lot of groundbreaking work.

Kelly Well, we have not cured prostate cancer yet and our objective is to find exciting new drugs that interfere with different pathways for the growth of prostate cancer. We are looking at drugs that interfere with new blood vessel growth prostate glands. We are looking at other growth factor inhibitors such as the insulin growth factor which may be pertinent to the growth of prostate cancer. We are also trying to understand some of the high-risk populations here. There are seven new genes that we are looking at. It is interesting, in Connecticut we have a very high-risk population of young people with high-risk for prostate cancer, and we have a large epidemiology study ongoing studying that in the State of Connecticut. That's what gets me out of bed every day, trying to understand prostate cancer, to understand the biology, and developing new therapies for the treatment of prostate cancer.

Chu If anyone is interested in learning more information about any of the clinical trials, how can they access that information?

Kelly They can call our offices at Yale Cancer Center and we will be more than glad to discuss any of the clinical trials we have.

Miller You mentioned insulin, what does insulin have to do with prostate cancer?

Kelly Insulin is actually a very important growth factor for multiple organs in the body, and this is important for multiple growths of multiple cancers, whether it is colon cancer or breast cancer. We know that prostate cancers, and other cancers, have these, what we call receptors on the cell surface and as insulin is secreted it actually attaches to the prostate cells and stimulates the growth of prostate cancer in differentiation of the cancer cells.

Chu As we were walking into the studio together this evening, Kevin was talking to me quite excitedly about a new clinical trial that combines chemotherapy with a treatment that actually targets this pathway. Kevin, can you tell us a little bit more about that study.

Kelly It is a very exciting study and we're cooperating with some of our industrial

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partners to develop a molecule called insulin growth factor antibody, and it blocks the insulin growth factor from getting into the prostate cancer cells combined with chemotherapy. We are very excited about these trials because these are exciting new drugs that we are bringing to Connecticut to help patients.

Miller Can you tell us more about the da Vinci robotic surgery technique?

Kelly As I said, the one standard therapy for prostate cancer is surgical removal of the prostate. Historically, it has been an open surgical operation, but we have developed ways to do it by what we call robotics, or a robot, that helps do it. The surgeon is actually behind an instrument panel and manipulates the arms of a robot that does the prostatectomy. The advantage of robotic prostatectomy is that you have small incisions, you can work in very small confined areas of the prostate and the area is magnified so you have a very detailed dissection of the nerves and all the blood vessels around the prostate. There is much excitement about the robotic prostatectomy; however, it does take a lot of skill from the surgeon to do these operations.

Miller It is interesting, because I am picturing this in a sense, as a form of microsurgery, but going directly after the cancer. You are doing that with your drugs now, which in a sense are more targeted also. Is that fair to say?

Kelly We are, but we are not quite there of late. There is advance in technology that we can actually improve it further, and I think in the years to come you are going to see much more targeted therapy.

Miller If you have to predict 10 or 20 years into the future, what would you say is the future of treatment for men with advanced prostate cancer?

Kelly I think we are going to have a much more targeted therapy looking at different pathways. We are going to have much more personalized medicine, where we actually look at the tumor, look at the patient and prescribe medications that are more exact for the patient and the tumor.

Chu One of the concerns the patients always tend to voice is about the side effects and toxicities associated with some of the therapies, the chemotherapies, and the newer therapies. How are we doing on that front?

Kelly We are making progress, I cannot say that we have developed the therapies and solved all the problems, but I think that we understand that elderly patients with prostate cancer are not quite the same as other patients. We have to understand how they metabolize drugs and use drugs differently, but we are much better off than we were 10 years ago. 10 years ago we did not have any drugs for advanced prostate cancer, now we have several drugs for advanced prostate cancer and

many more are under investigation right now. In the next 10 years I think you will see a lot of progress in the treatment for prostate cancer.

Miller I want to ask you about the topic of survivorship and the long-term issues men who have had prostate cancer face. Can you tell us a little bit about those?

Kelly The really interesting thing about prostate cancer is that it is such a heterogeneous disease. You can have patients with rapidly progressive disease that die within 2 to 3 years, but other patients can have prostate cancer for 10, 15, or 20 years. So, when you do treatments for patients who have long survivals, there are a lot of issues that you have to deal with over a 15-year period. You have to remember sometimes when you do treatments that it does impact their other comorbidities. You have to weigh the risk and benefits every time you do treatment for a patient on how it is going to impact to their overall life.

Chu In the last 30 seconds that we have, are there any key take-home messages that you would like our listeners to hear?

Kelly The message I want to give is hope. There is a lot of hope out there for prostate cancer patients. Understanding the disease is important, and getting a good physician who actually understands it can help you with the treatment decisions, and there are a lot of new treatments for you right now.

Chu This has been a terrific session and we look forward to having you come back on a future show to hear more about what is going on in prostate cancer. You have been listening to Yale Cancer Center Answers. We would like to thank our special guest, Dr. Kevin Kelly for joining us this evening. Until next time, this is Dr. Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions for the doctors or would like to share your comments, go to www.yalecancercenter.org where you can also subscribe to our podcast or find written transcripts to past programs. Next week, Ed Chu and Ken Miller will speak with the director of the National Cancer Institute Information Service at Yale, Linda Mowad. I am Bruce Barber, and you are listening to the WNPR Health Forum from Connecticut Public Radio.