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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 in honor of men's health awareness month, Dr. Anees Chagpar welcomes Dr. James Yu for a conversation about prostate cancer. Dr. Yu is an Associate Professor of Therapeutic Radiology and Director of the Prostate and Genitourinary Cancer Radiotherapy Program at Yale School of Medicine, and Dr. Chagpar is an associate professor in the Department of Surgery and the Assistant Director for Global Oncology at Yale Comprehensive Cancer Center.

Chagpar Dr. Yu, we talk about men's cancer awareness, and by far, I think the leading cancer affecting men is prostate cancer. Is that right?

Yu That's right. Prostate cancer is the most common solid tumor in men.

Chagpar What do men need to know about prostate cancer? Because it seems to me that almost everybody is getting prostate cancer out there.

Yu I think that is one of the things they need to know, that it is such a common cancer and that obviously it can be deadly. One in six men are diagnosed with prostate cancer within their lifetime, and the older you get, there are some studies showing that if you are in your 90s, you are more often than not to be walking around with a little prostate cancer. I think what men need to realize is that not all prostate cancers are the same. Most prostate cancers are very slow moving to the point that some medical experts do not think they should be called cancers at all, and then there is a subset of prostate cancers that can be deadly and need treatment, and it is differentiating between those that were working furiously on, but also requires a conversation with a physician.

Chagpar It sounds a lot like the same story with breast cancer, but the good news is that some cancers, you can pick them up early and get them treated and that is all there is to say about that. It is important to catch the bad ones, and some of the good ones, you do not need to treat. Is that pretty much it?

Yu That's pretty much it in a nutshell. The tricky part is a lot of the ones we do not need to treat are getting treated, either because the man or the physician is anxious about "letting a cancer go," and a lot of the ones that we would have loved to have treated earlier when it was in the curable form are spreading

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beyond our ability to cure, and that is the continuing work being done, trying to figure out who is the wolf and who is the sheep within the prostate.

Chagpar Let us talk about screening because it seems to me that a lot of this has to do with trying to pick up cancers early and the second part is figuring out which ones are the bad actors and which ones are not. So, who needs screening? When does screening start and how often do we do screening?

Yu Generally the folks that need screening are the people who are going to live at least 10 years from now.

Chagpar So everybody pull out your crystal ball, look in there and see whether you are going to live 10 years.

Yu That's exactly right, it is a very tricky thing to decide. But, men who are generally in good health and most guidelines say men in the age range of 55 to 69 should be screened. Now, there are some guidelines that push that even earlier up to 40, as young as 40 years of age requiring screening if they have a family history of prostate cancer and that is not your great uncle's cousins, that is a brother or father having prostate cancer.

Chagpar Even if your brother or father got prostate cancer when they were in their 90s?

Yu That is a good point. I would say if your brother or father got prostate cancer in their 90s, perhaps that does not count as a strong family history, that is just having an old man in your life or being of African-American ancestry is an indicator that you may have aggressive prostate cancer. And so the American Urological Association is actually pushing those men aged 40 and up to get screened, provided they can have a conversation with their physicians after screening about what it means to have an elevated PSA, what is the likelihood of having disease you do not really need to treat and being comfortable with having a diagnosis of prostate cancer but not undergoing treatment for it.

Chagpar In terms of screening, are we talking about PSA or just a digital rectal exam or are we talking about both? Are we talking about all kinds of fancy MRIs and ultrasounds and 3D imaging?

Yu In present day, we are talking about a digital rectal exam and a PSA blood test, which is what we are talking about as the standard of care screening. Sometimes the PSA misses a prostate cancer that the digital rectal exam will pick up, and sometimes the digital rectal exam misses something that the PSA will pick up. So, right now, we have to do both.

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Chagpar And how often do you do that?

Yu That is a good question. I think yearly or every other year would probably be sufficient in my opinion. I think at present most people are doing it yearly.

Chagpar So, if you are in your 40s, they are really only recommending screening for African-American men or those who have a family history?

Yu According to one guideline, right. And other guidelines like the US Preventative Services Task Force says start at age 55.

Chagpar Regardless of your family history or your race or ethnicity?

Yu Right. And they are not even saying start at 55, they are saying talk about it at 55, it is no longer forbidden. In 2012, the Task Force finalized their guidelines and gave PSA screening a don't recommendation. And recently, they are reevaluating that and publicly they came out and said, look we are reevaluating this for public comment, now we are considering and likely going to change it to talk to your physician about it at age 55 to 69.

Chagpar And so, when they said don't do and now are softening the edges a little bit, okay well maybe talk to your doctor, but do not necessarily do it, why is that? Because a lot of the general public, and I think a lot of our listeners, are sitting there saying to themselves, excuse me we have talked for a long time about the value of picking up cancer early, does PSA not do that?

Yu It speaks to the complexity of evaluating screening and proving that the screening saves lives.

Chagpar Okay, so does it?

Yu Based on a randomized trial in Europe, we think it does. The randomized trial in the US did not show that screening saved lives, but there has been a lot of criticism of that study because the arm that was supposed to not be screened was in reality prescreened. So it was a very messy trial to interpret. A lot of us are taking away from that there probably is a survival benefit and the study here in the States was flawed.

Chagpar In general, even though the USPSTF has said do not do the PSA and is now saying well, maybe we will adjust that and say talk about a PSA if you are 55 or older, are most oncologists and most urologists saying get screened?

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Yu Yes. I think most are. Studies looking at practice patterns after the USPSTF initial recommendations in 2008 and then again in 2012 looking at screening did show a decline, but in reality most people were still getting screened during that time because a lot of prostate cancer experts, a lot of oncologists, simply did not agree with that recommendation because of their own personal experiences with the difference between early caught cancer and later stage cancers.

Chagpar One of the questions that people ask is what is the downside to screening? Is there a downside?

Yu Of course, there is a downside. If you get diagnosed with a prostate cancer that does not need treatment or perhaps you could watch for a couple of years, but then you do decide to get treatment unnecessarily and you suffer harm from that treatment, then the screening has caused you harm down the line and

that is one of the reasons why the USPSTF and people who came out against prostate cancer screening were in favor of holding back screening. It is these downstream effects that can occur.

Chagpar So the treatment that resulted from the screening, but that goes to your initial point about not all prostate cancers need treatment. So, even though you get screened, the positive should not be "I got prostate cancer," the positive result should be "I have got a really bad prostate cancer that requires treatment," because if I have a prostate cancer, it may be that I have a prostate cancer that I can just sit on and watch and get checkups and I might be just fine, but I'm having the screening to make sure that I do not have one that is going to kill me.

Yu Right, people are trying to insert another step between PSA screening for any prostate cancers and treatment. Then, there is another level of diagnostic test to tease out aggressive or clinically relevant prostate cancer, and there are all sorts of companies in that space trying to market their particular molecule as being an indicator for higher risk disease. You can also try imaging the prostate before the biopsy and then there are many people after the biopsy where when you actually have that biopsied prostate tissue, trying to differentiate the actual prostatic tissue histologically or under the microscope. For the listeners who are not familiar with the medical terms, trying to tease out the aggressive prostate cancers at that point. So, there are multiple steps along the way. Pre-screening, post-screening, pre-biopsy, post-biopsy that you can insert a test, a genetic test or something to try and figure out who is the aggressive prostate cancer and who is not. Ultimately, the arbiter of whether it is an aggressive cancer or not is going to take the whole prostate out and look at it under the microscope, or time, time will tell and the treatment that you gave did not work and the cancer became metastatic,

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so we are working very hard to try and figure it out before you have to take the prostate out or radiate it, of course.

Chagpar Because I can just imagine a lot of our male listeners out there just rolled their eyes and said my choices are either take the prostate out or wait for this thing to spread really. So, let us go back a step to the screening part. I just want to tease out a couple of key pieces so that both I and our listeners are clear. When one guideline recommended screening younger for African-Americans, why is that? Do they generally get worse disease, are they genetically predisposed to get worse disease, is it that they just present later with disease, how much of that is racially mediated, how much of that is socio-economic.

Yu Right. So, we will try to tease that out, but epidemiologically African-American men do worse after a prostate cancer diagnosis likely due to later diagnosis of disease being a major part of it. And there may be more aggressive histologies also, more aggressive under the microscope types of cancer that are

more prevalent in African-American men as well. Because African-American men are doing worse, one of the ways that we are trying to improve that is to catch the disease earlier, and some people argue for more aggressive therapy, using more for example androgen deprivation therapy in combination with radiation and things like that, but because we cannot turn back the clock and improve outcomes for people years ago, we are trying to diagnose those cancer earlier.

Chagpar Okay. We are going to learn more about prostate cancer both in African-American and all other men as soon as we return from a short break for a medical minute. Please stay tuned to learn more information about prostate cancer with my guest, Dr. James Yu.

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move, speak, breathe and eat normally after surgery. This has been a medical minute brought to you as a public service Yale Cancer Center and Smilow Cancer Hospital. More information is available at [YaleCancerCenter.org](http://YaleCancerCenter.org). You are listening to WNPR, Connecticut's public media source for news and ideas.

Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest Dr. James Yu. We are talking about screening and treatment for prostate cancer, and right before the break, we were starting to understand or try to understand why it is that African-American men are recommended at least by one screening guideline to get screening earlier, and it is because I understand Dr. Yu that they present with more aggressive disease. What I am wondering is, if you took a group of African-American men and a group of Caucasian men, let us say, and they had exactly the same screening, they went for their screening starting at whatever age they are supposed to start and they got the same screening and they had exactly the same other health status, nutrition status, education, insurance, overall socio-economic status, would the African-American men still present with more aggressive disease. In other words, is this racial or is this socio-economic as a covariant that is often linked.

Yu Right, so it depends on which study you read and the studies have been

conflicting, and part of that is because it is so difficult to unpack the impact of race on cancer outcomes and we cannot randomize people the different races, we cannot take people, change them, and so in the US, as you know, health outcomes are so tightly connected to your access to care, your experiences growing up, your healthcare attitudes, and a lot of that is enmeshed, and so I do not know the answer to that question. Yeah, I do not know, all I know is that we need to do better for our African-American patients, and one of the ways that we are trying to is to recommend that they get screened earlier and being more aggressive in screening them.

Chagpar Okay. So, people get screened. If you are African-American or you have a family history, at least one guideline says start at 45 with PSAs and digital rectal exams annually, and the rest of the people start at 55. So, you go, you get your PSA, you get your digital rectal exam, and let us suppose the PSA is elevated, then what?

Yu So, if your PSA is elevated, you typically will get a confirmatory one as well and if both of them are elevated, then you have a discussion with your doctor about whether this leads to a biopsy or not and what are your attitudes and what are you going to do if you get a prostate cancer biopsy and kind of prep you for the idea that it could be something you do not need to do anything about.

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Chagpar But if you have done the PSA and it is positive twice, is there a reason why you would not do a biopsy.

Yu I guess if you are very much against any sort of instrumentation of your prostate because you have not had a cancer diagnosis yet.

Chagpar Then why would you do the PSA?

Yu Because it is a very simple, a lot of men actually get PSAs without knowing that they have had PSA, it is part of their blood panel, cholesterol, etc., and it just kind of comes out.

Chagpar So, let us suppose that you are an informed patient, why would you get a PSA if you are never going to follow the next step, right? It is kind of like getting a mammogram every year but then saying there is something there, I do not want to know what that is, then it is kind of like why do you have the mammogram and expose yourself to radiation and incur healthcare cost. So, let us suppose that you have a positive PSA x2, the conversation with your doctor is, I have an elevated PSA, it is time to go get a biopsy, how do they what to biopsy?

Yu Well, most places around the country will do a random 12 core biopsy of your prostate.

Chagpar Just like blind?

Yu Just like blind, yes.

Chagpar That is so scary, I cannot even tell you.

Yu Here at Yale and lots of other people, we do an MR-guided biopsy as well. Dr. Sprenkle and folks over in the urology department are one of the earliest adopters of this targeted biopsy, and so typically we do that in addition to the 12-core biopsy. I do not know, Dr. Sprenkle can clarify this at a later point. They may be going more towards the targeted biopsy by itself.

Chagpar So, is the philosophy there that you will find abnormal cells no matter where it is in the prostate that you take this biopsy from if your PSA is elevated?

Yu Right, it is the idea that the entire prostate has been exposed to the same testosterone.

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Chagpar So, it is not like there is a particular area. So, in the breast, if you were to do a biopsy with your eyes closed, that would not work.

Yu Right. Traditionally, it is a random, well not random, but taking a little chunk out of different pieces of the prostate systematically.

Chagpar So, they undergo this biopsy and then it comes back cancer, but all cancers are not the same.

Yu Right. So, the prostate cancers are typically graded per something called a Gleason score. So, under the microscope, how aggressive the prostate cancer looks and you get two numbers – the primary and the secondary Gleason score, meaning what is the most prevalent pattern that is the first number and what is the second most prevalent pattern, and it is 1 through 5 for the primary and then 1 through 5 for the secondary and they add them together for the final Gleason score. There are some nuances in there as well because a 3+4 is not the same as a 4+3 and there is a new grading system out well trying to differentiate between those.

Chagpar Right. So, the rules of mathematics cease to exist in prostate cancer. But somehow, you end up with a final score. Then what happens?

Yu So, once you get a final score, if you have a high Gleason score, so 8, 9s or 10s, typically those will also undergo staging with a CT scan of the abdomen and pelvis and maybe also a bone scan. If your Gleason score is a 6 and your PSA is under 10, you do not necessarily need staging at that point because the likelihood that this disease has spread is very low. So, in the community that may be all there is to it. There may be a role for MRI as well to look at the prostate and see how far outside of the prostate any cancer has gone now. MRI has not disseminated completely throughout our listening universe but we are doing that more and more here because it is useful for staging the prostate in an even more granular way than just a CT scan.

Chagpar Okay. So, 8, 9 and 10, they scan your whole body and see if there is cancer anywhere else, and if it is anywhere else, then that is metastatic disease, and you do not want to be there? You would rather be in localized disease.

Yu Right, and the vast majority of prostate cancers are localized.

Chagpar So, when you are 6, do all 6's get treatment?

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Yu No. I think if you have an initial diagnosis of Gleason 6 prostate cancer and a low PSA, you should have a frank conversation with your physician and try to air on the side of being conservative and not treating the prostate cancer. If it is a true Gleason 6 prostate cancer, it is very, very, very unlikely to cause death from prostate cancer.

Chagpar Okay, but I can imagine that a lot of people who are listening to this going, I have a number 6, and you are telling me that you would veer towards, pretty much watchful waiting, but if I had an 8, 9 or 10, you would be worried about this spreading all over my body. That is the difference of like 2 numbers, and I understand that mathematics ceases to exist in prostate cancer, but that is pretty scary. So, how do you follow a 6 and how do reassure gentleman who have a 6 that their prostate cancer is not going to kill them.

Yu So, you follow a 6 with repeated imaging of the prostate, well here at Yale, we follow them with reimaging with an MRI and re-biopsying the dominant tumor with a targeted biopsy or you can also just follow them with their PSAs, because the PSA is actually for Gleason 6 prostate cancer a very sensitive indicator of prostate cancer burden. And if the PSA remains low, then you can biopsy in a couple of years and then if the gentleman is 85 and their PSA is kind of poking along and they are fine and they just have a Gleason 6 diagnosis, then you just leave them alone?

Chagpar Leave them alone and live their life.

Yu Yes, that's right.

Chagpar And if their PSA goes up, well then you treat.

Yu Then, you can look for the source of the PSA.

Chagpar What about a 7? We went from 6 to 8, 9 and 10. I noticed that 7 was missing.

Yu So, 7s are the most common, unfortunately, and the 3+4s, there is research at MD Anderson and Sloan Kettering that 3+4s we call low intermediate risk, and the 4+3s we call high intermediate risk, and the difference there is relevant for radiation therapy and whether you recommend the use of hormone therapy in conjunction with radiation or not. But those Gleason 7s I believe do require treatment, those are the ones that may lead to prostate cancer death or



metastatic disease and are typically caught early enough that treatment will be successful.

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Chagpar So, a 7 needs treatment and an 8, 9 or 10 that has not spread all over your body also needs treatment?

Yu Also needs treatment, absolutely.

Chagpar So, how do we decide what kind of treatment? Like I mean, do all of these guys get their prostate out?

Yu Right, so deciding what treatment that a patient gets depends on how healthy they are, whether they are surgical candidate. What I think the likelihood of regional disease or disease outside of the prostate is, it is my personal belief that the high-risk patients should get at least a radiation oncology consultation, but I would prefer that they receive long-term hormone therapy in combination with radiotherapy because I think treatment for prostate cancer that may be more regional. Now, that is an academic discussion that I continue to have every day with our urologists who I think rightly know that if they can get the prostate cancer out, they could potentially spare the patient 18 months of hormone therapy, and I think that is a valuable endpoint. The tricky part is that we do not know, there has not been randomized trial showing one is better than the other, and in my opinion if you get surgery and the cancer comes back, you will need radiation anyways and the combination of the two therapies obviously has the side effects of the combination of the two therapies, which is more than either one by itself.

Chagpar So, the options are surgery or hormonal therapy and radiation.

Yu For the high-risk folks, that is correct. Every now and then, as someone who is risk, who is not healthy, cannot tolerate hormone therapy, that we just treat with radiotherapy alone, but I think that is a suboptimal treatment.

Chagpar And so, the difference is then surgery versus radiation. And so if you are healthy and you are a surgical candidate, is veer for one or another.

Yu So, I am a radiation oncologist obviously in my opinion I think the surgical candidates are the healthy intermediate or low-intermediate risk patients. I think folks with low-risk prostate cancer should not be getting treatment upfront, they should be followed, and honestly the low-intermediate and high-intermediate patients I think could arguably get radiotherapy as well and there was a randomized trial in the intermediate risk space, the Protect study, which compared patients who had a prostatectomy to those who had 6 months of hormone therapy and radiation and found no difference in survival. So, I think a cancer control, the two are equivalent. The only differences are their side effects.

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Chagpar So, talk to your doctor about the side effects.

Yu Talk to your doctor and if you have not seen a radiation oncologist, I would encourage you to do so and if you have not seen a urologist, you should do so as well and get both sides of the story.

Chagpar So, tell us a little bit about the side effects of both.

Yu Sure. So, surgery places you at risk of urinary incontinence, urinary dribbling, and radiation causes you the risk of having rectal irritation, bleeding and also will impact your urinary control after surgery because radiation can cause stiffening of the tissues, stiffening of the urinary sphincter and cause a little bit more dribbling after surgery. So, if you can avoid one of two, I would highly encourage it as opposed to getting the two at the same time. That said, for some people, we have to do both because they have had surgery, they have prostate cancer recurrence and radiation remains the only chance for cure after prostate cancer recurrence.

Dr. James Yu is Associate Professor of Therapeutic Radiology and Director of the Prostate and Genitourinary Cancer Radiotherapy Program at Yale School of Medicine. If you have questions, the address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and past editions of the program are available in audio and written form at [Yale-CancerCenter.org](http://Yale-CancerCenter.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.