Prevention and Diagnosis of Prostate Cancer

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I have been tasked with discussing prevention and diagnosis of prostate cancer. The title of my talk is The Diagnosis and Prevention of Prostate Cancer: A Challenge for the 21st Century Man. I have been very distressed as a urologist seeing all of the mixed messages regarding how to use PSA. You have about five governmental organizations that have put out five different positions on prostate cancer early detection; I think it is important to try to tease through the mixed messages for a general consensus.

Based on the American Cancer Society data, for 2010, there will be nearly 217,000 men diagnosed with prostate cancer, and about 32,000 men will die of prostate cancer this year. There are currently two million men living in the U.S. with prostate cancer. The five-year survival rate is now almost 100%, and the ten-year rate is 91%. Survival rates for African-Americans still remain lower than Whites for all cancers. The incidence of prostate cancer amongst African-American men is about 73% higher than White men, and mortality rate is almost 2.5 times higher. Even though we have seen an improvement in detection and improved survival, the disparity in the Black community remains.

What is this higher incidence and why do we die more? Is it access to care? Possibly. Is it attitudes about care? Possibly; that has improved but we still have a long way to go. Are there socioeconomic and educational differences? Yes. Are there differences in types and aggressiveness of treatment? Somewhat, but I think the playing field is being leveled such that most treatments are available to everybody, but you can lead a horse to water; you can't make him drink. Are there genetic differences? We have seen there definitely are genetic differences. Are there dietary differences? Definitely.

African-Americans with advanced cancer have exhibited a lower socioeconomic status. They tend to be underinsured, and they tend to participate less in early detection. Are there biological differences in disease behavior? Definitely: we see prostate cancer being diagnosed at an earlier age. Studies have shown definite differences in the pathological type of prostate cancer, tumor volume versus the PSA level, differences in androgen receptor pathway, and there are likely modifiable factors that affect gene expression: diet, obesity, possibly environmental factors, where you live, your environmental exposure.

The biggest question right now is whether or not to screen. I do not like screening; I like early detection. Whether or not we should be engaging in early detection of prostate cancer, my personal position is definitely, but there are several studies that most clinicians have followed that have tried to answer the question. Trials include the Quebec [phonetic] trial, the Labri [phonetic] trial, that looked at 46,000 men; the Tyrol [phonetic] study in Austria that looked at 21,000 men; the very large European study screening for prostate cancer that looked at 162,000 men; and the PLCO cancer screening

trial looked at over 154,000 men. Did these studies succeed in what they set out to do? Some criticisms with the Quebec study are that the study was not done in the U.S. but rather in Canada; there are concerns about how it was designed; and there is an absence of men of African descent in that study. The Tyrol study was done in Austria; some of the concerns are obvious. The follow-up period was not long enough, and there is a complete absence of men of African descent. The European study had a follow-up period that was inadequate to assess the mortality impact, and the absence of data on men of African descent was pretty significant. Criticism with the PLCO study is that the follow-up period was not long enough, and there is an absence of data analysis in African-American men. Thus, there is a consistent issue, and yet, these studies are being used to make policy in the U.S.

There were some benefits from the Canadian study. Unscreened men had a 41% death rate versus 13% in the screened population, which yielded an odds ratio advantage of 3.85. If you were screened, you had an almost four times chance that you would not die of prostate cancer. Six deaths out of the 7200 screened men occurred versus 69 out of the 14,000 controls, meaning 82% fewer deaths. Even when you corrected for the four- versus seven-year follow-up period, there was still 69% fewer deaths in the screened population. In the screened population, low stage cancer detection was enhanced, stage migration was clear, metastatic disease at diagnosis was reduced, so it suggests that there is survival benefit associated with being screened.

Findings from the European study: even though there were not any men of African descent in this study, 5900 cancers were found in the screened men versus 4300 in the controls; the cumulative prostate cancer incidence was 8.2% versus 4.8%; 71% more cancers were found in men who underwent early detection; 72% of the men who were screened had a lower Gleason score, meaning less than or equal to Gleason six, versus 55% of the control population; 45% of the controls had high Gleason scores, meaning greater than or equal to Gleason seven, versus 28% of the screened men, meaning that local disease was favored in men who underwent screening. There was a 20% reduction in deaths in the screened group versus the controls.

This is from the U.S. Preventative Service Task Force. It has been published and these are the guidelines that ultimately insurance companies, Medicare, et cetera, may base their policies when determining what they will/will not cover. The task force said the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than 75 years. So they basically recommend against any prostate cancer early detection in men over 75, which I disagree with; we have men who are living into their 90s who have as much of a right to know that they have prostate cancer and be offered the option to be treated as a younger man.

The biggest question right now for all men of all races in America is who should they listen to and what should they do? Should you listen to the U.S. Preventative Services Task Force, the American College of Preventative Medicine, the National Comprehensive Cancer Network, the AUA, R. Frank Jones [phonetic] Urological Society which represents the African-American urologists in the country, or the ACS? And I think we can, at the end of this, come to a decision about who has the best policy.

The R. Frank Jones Urological Society, for which I am the immediate Past President, and the UAU, we all have this as our guideline, and I think for most American men, this is probably the best policy surrounding PSA screening. A thoughtful and broad approach to PSA is important. The age for obtaining a baseline PSA should be 40 years, meaning that you should get a PSA baseline in order for you to know, as you get future PSAs, whether or not your PSA is rising significantly. You need more than just a set number, and we have been using 2.5 as the upper limit of normal for men under 60, and 3.0 for men over 60. But Ian Thompson [phonetic] has shown that even at much lower PSAs, you can be found to have an aggressive prostate cancer.

In looking at your PSA value, you need to look at everything: digital rectal exam, free and total PSA, your age, PSA velocity which is the rate of increase meaning the change in PSA value from 12 months before, PSA density, family history, ethnicity, prior biopsy history, and comorbidities.

Recent studies have suggested that PSA screening leads to overdetection and overtreatment; in some patients, that is true. But as an educated consumer, I think all of us have a right to know if you have something and be given the option to undergo treatment or not. That is my position, and that is basically the position of the American Urological Association.

Prostate cancer prevention is being evaluated in multiple trials. For the SWOG and the toremifene studies, the data is not out yet, but looking at the Prostate Cancer Prevention Trial, the SELECT study and REDUCE trial, we have enough data now that we can draw some conclusions. The Prostate Cancer Prevention Trial looked at prostate cancer prevalence during seven years. This study was published in the New England Journal of Medicine in 2003. They showed in the placebo arm a near-25% reduction in prostate cancer in men who had been treated with a 5-alpha-reductase inhibitor.

With the tumors that were discovered, there was some controversy over possible upstaging of the cancer after exposure to finasteride, but after reevaluation, that is felt to be an artifact. The drug is safe, it has minimal sexual side effects, and many men are being treated with it for enlarged prostate.

This led to the REDUCE trial, which was an improvement over the PCPT trial. It was a four-year multicenter international randomized double blind study looking at dutasteride, which is also known as Avodart; it inhibits both receptors. It is a 0.5 mg dosage, and this was that versus a placebo. They looked at patients who had high risk for prostate cancer, meaning PSAs of 2.5-10 in men 50-60 years, and PSAs of 3-10 for men over 60 years. A single negative biopsy was required within six months of enrollment to establish a baseline, and the primary endpoint was a biopsy detectable prostate cancer at two and four years of treatment.

The conclusion: dutasteride showed a 23% reduction in prostate cancer over placebo. A very safe medication, similar to Proscar, which leads to the question, is this a drug that every man who is at risk for prostate cancer should be taking?

So after evaluating all of the data, Ian Thompson and others have come to these conclusions. A man who is 55 years old, with a prostate volume of 40 (enlarged) and an AUA symptom score over ten, who has risk factors for prostate cancer, be it family

history or being African-American, who has had an elevated PSA, maybe a negative biopsy, male pattern baldness, and is concerned about prostate cancer, and possibly already on the alpha blocker: this is the best candidate for chemoprevention.

My personal position: I have a family history of prostate cancer, my father's brother had prostate cancer, I have a cousin with prostate cancer, I take Avodart every day. After reviewing the data, I think the side effects of concern are whether or not it may affect your erection, there is a very low incidence of sexual side effects, but I think the benefit of the protection that it may infer is reasonable. So if you are a high risk male, I would strongly consider discussing this with your urologist to see if this is something for you. And if you have a family history, and you have young men in your family who are at that age of risk, they may consider doing this.

The AUA and ASCO have made a statement regarding chemoprevention that men with a PSA score of 3.0 or below, who are screened regularly or plan to get an annual PSA test, and currently show no signs of prostate cancer, should talk to their doctor or urologist about the risk and benefits of taking a 5ARI to further reduce their likelihood of getting prostate cancer. Men who have already taken a 5ARI for enlarged prostate should talk to their doctor about continuing this medication for the prevention of prostate cancer. I think that is a very responsible approach to chemoprevention.

Another study is the SELECT trial; I was one of the principle investigators. This was to take a look at selenium and vitamin E in combination as a prevention for prostate cancer. The study started back prerandomization 2001-2004. There was a prerandomization period which led to the patients being randomized into four arms: placebo, placebo plus selenium, vitamin E plus placebo, vitamin E plus selenium. Ultimately, the study was closed out early due to findings that vitamin E may lead to an increased risk of cardiac side effects. So the data that they had was evaluated, and the bottom line is that vitamin E and selenium were shown not to have an impact on preventing prostate cancer.

In approaching patient management as it relates to PSA and prostate cancer and evaluation, patients should be referred to a urologist when using a prostate cancer risk calculator, if found to be in a high risk category, if they have an abnormal PSA velocity regardless of the level, if there is an abnormality detected on DRE, if patients are failing treatment for an enlarged prostate, and patients with hematuria.

The take-home messages of my talk are that age, race, and family history are significant risk factors for prostate cancer, and should be a major role in evaluation of an individual, or as an individual, to make a decision to undergo evaluation for prostate cancer. Prostate cancer screening has certain negative side effects if a patient has to undergo an evaluation, but the primary risk with a prostate biopsy is sepsis, which is less than 1%. We perform thousands of biopsies annually, and very few patients become significantly ill or have major side effects from a prostate biopsy. The major issue is that it can be painful, and guys do not like it. But it is reasonable to undergo a biopsy to know whether or not you have an abnormality; then you can make a decision on whether or not you want to undergo treatment. I think the annual DRE and PSA is a reasonable part of the male exam; it is important to get a baseline evaluation when you turn 40 regardless of whether you are Black or White, so that you have a baseline value from which to base upon any future evaluations as you go through your annual checkup; the AUA guidelines

are a perfect way to approach the use of PSA and the DRE; the results of the PCPT trial and the REDUCE trial show very promising results, and if you are in a high risk category, you should consider and discuss with your urologist the use of a 5ARI to reduce risk of developing prostate cancer.

Male Participant

I was recently diagnosed with prostate cancer. My clinician could have done a better job to educate me. I elected to have a radical prostatectomy simply out of ignorance. I thought if the prostate was removed, the cancer itself would have been removed, but I was wrong. We need to have better patient education in this day and age.

Male Participant

I am a prostate cancer survivor. How useful is vitamin D?

Dr. Stone

Some data show relationship between vitamin D deficiency and prostate cancer; that is the new frontier.

Male Participant

What are your thoughts regarding early prostate antigen II as a possible replacement for PSA?

Dr. Stone

At the AUA, there have been a host of new markers that were supposed to possibly replace PSA or improve PSA. There were a couple of markers which might come out of Baylor from a friend of mine, but thus far, none of these new markers have panned out yet because you need to evaluate these markers in such a very large population of men before you can offer it to the general population. I think based on the experience with PSA, basically, PSA was developed on a very small number of White males and then released to the general population, and later, discoveries were made that cannot be consistently used in different races, we had racial differences in PSA levels, the relationship between prostate cancer and BPH, so to avoid arriving at where we are now with the current PSA that we have, I think it is too early to make a comment about that marker. We will just have to wait and see. PSA is not the perfect test, but without it, a lot of people would have died.

Male Participant

What percentage of men who have had radical prostatectomy have it done through the rectum?

Dr. Stone

You do not do it through the rectum, but there is a perineal prostatectomy which I do; I was one of the only guys in New York doing the perineal. The perineal is an excellent approach, however, the ability to do a good nerve-sparing procedure from that approach is limited because you are able to see the nerves, you can separate them, but you have to retract the nerves throughout the procedure in order to get the prostate out. Any type of manipulation of the nerves reduces the likelihood that you are going to be potent even

after you save the nerves. Even now during robotic surgery where you have magnification eight times normal, you can beautifully separate the nerves from the prostate, yet, post-treatment potency is still not that great. Being overweight makes it a struggle.

Male Participant

What does it mean when a clinician says that the prostate state is nothing to worry about right now?

Dr. Stone

The relationship between the size of the prostate and having symptoms is all over the place. You can have a man with the biggest prostate you have ever seen, but he is totally asymptomatic; you can have a man with a very small prostate who is significantly obstructed. So the rectal exam itself, by saying it is enlarged, does not mean much, and that is where the AUA symptom score, which is a questionnaire that most urologists will have you fill out so you can kind of know where you are as far as symptoms, helps you make a decision as to whether or not you have minimal symptoms, moderate, or severe, and that is more important than size. Now, size can become an issue in interpreting the meaning of PSA.

One of the biggest dilemmas faced by urologists are the guys who come in with, say, a moderately abnormal PSA, they have a biopsy that is negative, yet the PSA keeps rising. The guy is terrified because he is thinking he might have prostate cancer, you are doing biopsies yet they are coming back negative, and at what point, what do you do? BPH, or enlarging cells, elevate PSA; this is where Avodart or finasteride can help out. These medications block the conversion of testosterone to dihydrotestosterone, which is the active form that stimulates prostate growth; you will see a reduction in prostate volume of roughly 30% and up to about a 50% reduction in PSA. In this gentleman who has his rise in PSA, if that PSA drops to about half, you can relax and say, okay, his rise in PSA is more than likely related to prostate enlargement. In a man who has prostate cancer, if the PSA is continuing to rise through exposure to the Avodart, you probably need to be a little more aggressive about your biopsy technique. There will still be a population of guys with rise in PSA that you cannot identify where it is coming from, and this is where PSA is not perfect. That is one of the big dilemmas in urology; a biopsy is not a fun thing, and it is not something you want to go through.

In response to another audience question, the prostate basically has two zones: the transition zone, which is the core of the prostate, and the peripheral zone. We are classically taught that the majority of cancers occur in the peripheral zone, but there are individuals who have tumors that occur in the transition zone. PSA has allowed us to detect most cancers before they become a nodule; however, there are individuals who have normal PSAs that can have a tumor that does not express PSA and may have a nodule. The combination of DRE and PSA should continue, and I am troubled when I see screening or early detection programs that are PSA only because that sends the wrong message that you do not need to have the rectal exam done. As a urologist, I am biased; I think the DRE is a very important aspect of the male examination.

Male Participant

There are men who will not allow you to do a DRE on them. I reluctantly have had to take the PSA as partial baseline in these men, and take it again the following year, and if there is a rise, then it becomes the duty of the urologist, or whoever, to convince the patient of the DRE and whatever follows.

Male Participant

Regarding ultrasound imaging, is that finding used as another diagnostic tool?

Dr. Stone

Ultrasound assists us in doing a biopsy. A big study was done at the University of South Alabama looking at PSA, DRE, and ultrasound and concluded that ultrasound cannot diagnose prostate cancer; there is no unique echo pattern belonging to prostate cancer. Ultrasound assists in performing a prostate biopsy and calculating prostate volume but it is not useful as a tool for imaging prostate cancer.

Male Participant

What is the correlation or relationship prostatitis and prostate cancer?

Dr. Stone

The relationship is that prostatitis is an inflammatory process that can make the PSA be elevated. PSA is not a perfect test. PSA can be elevated due to various issues: enlargement and also inflammation. Prostate cancer is typically asymptomatic, which is why it is so important to get the DRE and PSA. Men who are symptomatic typically have very high PSAs and pretty significant cancers.

Male Participant

Given that heterosexual males have this taboo about getting a DRE, if there is a slight elevation in PSA level, is it up to the urologist to suggest that now a man needs to think about the DRE as a follow-up?

Dr. Stone

There are only about 250-300 African-American urologists out of the 10,000 in the U.S. When there is a connection between a clinician and a patient, such as when both are African-American, the clinician is much more successful in getting that patient to cooperate and do things which the patient may not otherwise do, such as getting a DRE done. Finding the right clinician who can have the right type of dialogue is so important in getting evaluations done and getting patients to be compliant and follow-up. Support groups present a double-edged sword but can be useful. It is important to ask questions and get second opinions such that the patient is very comfortable with the choice or decision he makes.

Male Participant

I commend women for coming out and being concerned about their health, for instance, in the women's health conference across the river here. I believe for years, men have been neglected as far as any kind of publication and as far as advertisement, as far as male issues are concerned. It is nice to see that this forum is designed to start to recognize some of the issues of men's health, and I am hoping that this will be an annual

event to get more people informed about their health as far as prostate and any other ailments that plague our community. With respect to the order of the PSA test, what would be the method of diagnosis? Would you do the PSA test, then second, would you go to DRE?

Dr. Stone

In my office, I have the blood drawn first because there have been studies that suggest that a DRE may cause an elevation in PSA; I do not necessarily agree but that is how I do it. A man should get baseline PSA at age 40; that goes for all men. You should involve a urologist who is an expert in the management of prostate cancer, and if at any point you are not happy with the course of treatment, get a second opinion. I have been lobbying in D.C. for health policy, and what I have seen is that the lobby for breast cancer is very powerful; the lobby for HIV is very powerful. Individuals who have been affected by those conditions have been organized; they have had a significant impact on policy as it relates to funding and decisions about treatment, et cetera, because of their lobby. The male lobby for prostate cancer, you can barely hear anything. Now, we are trying to get onboard. A man should have the option to get a DRE and PSA and have it paid for by his insurance coverage once a year.