Prevention Strategies

Ian Thompson, MD

I. Prostate Cancer Prevention Trial

The Prostate Cancer Prevention Trial is the first of the large-scale prevention trials. It randomized men who at the time it was felt that they had a very low risk of having existent prostate cancer with a PSA less than three and a normal rectal examination to finasteride or placebo, followed them every year for a rectal exam and PSA. Based on that, a biopsy was recommended if either were abnormal, and at the end of the study to ensure that all of the potential biases associated with rectal exam and PSA were attended to, all men were recommended to have an end-of-study biopsy after seven years of exposure to finasteride.

In the trial, 24,000 men were enrolled and 18,882 were randomized. The men were recommended to have a biopsy in the placebo group if their PSA exceeded four, and in the finasteride group the same fraction of men were also recommended to have a biopsy on an annual basis to make sure there was the same likelihood of a biopsy in both groups. At the end of the study, the final results showed that the cancer reduction was 24.8% for all cancers. There were significantly fewer cancers overall, and the majority of the reduction was with Gleason 5 and 6 tumors, which are the bulk of cancers that are detected today. In Gleason 7 tumors there was no difference, but there was a statistically increased risk of high-grade cancer. You can see that there were 47 more high-grade cancers and 350 fewer cancers overall.

II. Finasteride Effect

We now understand why this is, and the interesting thing about this agent is it reduces your risk of getting prostate cancer by about a quarter, so with about 200,000 men per year diagnosed with prostate cancer if finasteride were widely available there would be 50,000 men per year in the United States not diagnosed with prostate cancer—presumably a good thing. The other fascinating thing about this drug is it increases the ability of PSA to detect cancer and aggressive cancer, and the reason for that is that most elevated PSAs are not due to prostate cancer. They're due to BPH, prostate enlargement. Finasteride makes those PSAs go down. If you have prostate cancer and your PSA is elevated as a result, your PSA goes down less. It actually makes PSA a better test. If you have a prostate cancer, your doctor is more likely to detect it with a rectal exam, and finally, by making your prostate smaller, you heard Dr. DeMarzo talking earlier about when you do a prostate biopsy you are only sampling a very small amount of the prostate, finasteride, Proscar, shrinks the prostate and in so doing it increases the likelihood if you put a needle in the prostate if cancer is present that you'll find it. All three of those things dramatically change your ability to find prostate cancer and high-grade cancer.

If your doctor uses a PSA of four to prompt a prostate biopsy, you'll see that it actually only finds 24% of the prostate cancers. If you use the same number of biopsies, so the specificity is the same because PSA goes down with finasteride, you will use a cut point of 1.6. You'll increase the sensitivity from 24 to almost 38% coming close to a 60% increased likelihood of detecting it. For high-grade cancer it

increases from about 40% to 53%. It increases the likelihood that the PSA will be abnormal and prompt you to recommend a biopsy.

The sensitivity for the rectal examination for the detection of prostate cancer goes from about 16% to 21%, and it also doesn't prompt any more unnecessary prostate biopsies. Finally, when you do a biopsy of the prostate and subsequently a prostatectomy is performed, you may say, oh my goodness, it was a low-grade cancer on the biopsy but you find high-grade cancer on the prostatectomy. That happens about 30% of the time. One of the biggest problems is the man in whom you do a biopsy who has an aggressive cancer in the prostate and you miss it. It turns out aggressive prostate cancers in this study, the largest study ever done for this purpose, were missed half the time. If you are on finasteride because the gland gets smaller, if you have an aggressive prostate cancer, you find it 70% of the time, increasing dramatically the likelihood that you can find it. The overall risk reduction is about 30% for prostate cancer. Cancer reduction is the top one; 0.7 means there is a 30% reduction in prostate cancer. Low-grade cancer, Gleason 6 and less, is reduced by about 32%, and high-grade prostate cancer is reduced by about 28%, substantial reductions.

III. Side Effects of Finasteride

In terms of the side effects of the drug, there were some good side effects. It grows hair on your head. It improves urination, and it cuts a man's likelihood of needing an operation on the prostate for prostate enlargement or for going into retention as we get older in half. In terms of bad side effects of the drug, one is about a 1% risk of breast tenderness. The second thing is that the ejaculate volume is reduced. So, if you measure the volume of the ejaculate, it is reduced. In terms of sexual function, there is fundamentally no difference with the medication. The medication is now generic, and the cost is about $30 a month if you shop around.

IV. Dutasteride

Dutasteride data were just presented in a study of men who had elevated PSAs and a negative biopsy, and the evidence would suggest about a 22% reduction in risk of prostate cancer in those men.

V. Complementary Medicine, Nutrients and Diet

We think that fat, especially the bad fats, increase the risk not of prostate cancer but of aggressive prostate cancer. There is a fair amount of evidence to suggest that. Calories are also associated with the risk of prostate cancer, and the more obese we are, the higher insulin levels are, which are related to the risk of developing prostate cancer. The other very tragic thing is that as we become more obese our PSA levels are artificially reduced. If you do PSA screening in obese individuals, you need to adjust the PSA for detection because if you use a standard cut off of four, you are effectively delaying the diagnosis of the disease.

The challenge is that every time we have looked at complementary medicine, nutrition and diet, we can't reproduce the observations that are made in animal models in an epidemiologic study. In terms of dietary recommendations, we tell our patients with regards to prostate cancer we can't tell someone if you do this from a dietary standpoint we know it will reduce your risk of prostate cancer. On the other hand, we do know that there are dietary practices that make you live longer and live healthier—exercise, weight reduction, caloric restriction, increasing the consumption of fruits and vegetables,

decreasing the amount of meats and fats, those things make you live longer, make you live better and protect against heart disease and stroke. Even if they don't reduce your risk of prostate cancer, they are a good thing overall because we always forget that a man who is born in the United States if he is Caucasian has a 3% risk of dying from prostate cancer. If he is African American, it is 4%. Most of us don't die of prostate cancer.

Given the choice of treating the disease when it is metastatic, finding it early and treating it, or never having it in the first place is a no-brainer. I choose the third, and I am actually taking finasteride myself.

Questions

Brian Stone, MD

I'm 49. My Dad's brother died of prostate cancer. My second cousin died of prostate cancer, and I've heard that we had a great uncle with prostate cancer. I've read all the data, and I've started myself on dutasteride. Reasonable or unreasonable?

Ian Thompson, MD

It's very reasonable. I chose myself to start taking finasteride. I am in my own biomarker study so I get my PSA drawn on an annual basis. Personally, I don't want to have to come see me and have a prostate biopsy. Most biopsies are unnecessary because the PSA is up or the rectal exam is abnormal and it's not related to prostate cancer. I personally don't want to have a prostate biopsy, come see you, and you tell me, oh thank goodness, your biopsy is negative. Okay, well I didn't need it then, and I also don't want to have a biopsy that shows prostate cancer. We're both doing the same thing. I strongly believe in prevention.

Participant

Is there a recommended age for starting on a 5-ARI?

Ian Thompson, MD

I started when I turned 55 because that was the study design, and prostate cancer is distinctly uncommon before 55. African American men get the disease about five years earlier, so they may want to start at 50. If you have a first-degree relative and you're African American, maybe start at age 45, something like that, and the other question is do you want to treat everybody? If a man comes in at age 70 with a PSA of 0.5 and nobody in the family had prostate cancer, you will probably have to treat 100 to 150 men like that to prevent a prostate cancer. Whereas if a man comes in with a PSA of 2.5 or 3, you might have to treat only 8 or 9 of those men to prevent a prostate cancer. It might be economically more advantageous to treat higher-risk men, but we also have to remember that most men who have prostate cancer and die of prostate cancer have no risk factors.

Brian Stone, MD

The U.S. Preventative Services Task Force is recommending that PSA screening not be done. It has certain political ramifications with insurance. What's your position?

Ian Thompson, MD

I think that's irresponsible. I also think that lining people up and doing PSA screening without informing them is irresponsible. Personally, I think people should be offered the opportunity and told about the pros and cons. The big problem that I see is that people are not informed. Primary care physicians have no time. We have no time, and properly informing people so they can make a smart decision takes time.

Participant

Can you explain the number needed to treat to prevent a case of prostate cancer?

Ian Thompson, MD

The studies that have been done are studies with an end point of prostate cancer diagnosis. A study to address the question of survival or mortality from prostate cancer would be between 60,000 and 100,000 subjects in size and would have to be 25 to 30 years long. In this time of budgetary constraints, I don't think we will see that. Ideally, we would like to know that we're preventing death from prostate cancer, but most people who have prostate cancer will never die from it. Most of the burden from prostate cancer comes from the treatment.