DR. FRITZ SCHRODER

*Dr. Fritz Schroder is Emeritus Professor of Urology at Erasmus University Medical Center in Rotterdam, the Netherlands. He is author and co-author of more than 650 peer-reviewed publications and 197 book chapters and editor of 21 monographs.*

He spoke with Prostate Forum about the 13-year results of the European Randomized Screening Study on Prostate Cancer as well as his trial, published in 2013, on using Avodart use to prevent and treat prostate cancer.

PROSTATE FORUM: Can you tell my readers about the progression of your career?

DR. FRITZ SCHRODER: I started my training as an urologist at UCLA in Los Angeles in 1967. I was accepted there as a first year associate resident. I was very happy to be among educated young people; most prominent was my first year co-resident, Patrick Walsh, who later became Professor of Urology at Johns Hopkins University. We became-as we say to each other and we write to each other-best friends, because we have many professional and personal contacts in common. We even go on bicycle tours together.

How did I get involved with prostate cancer? I was sent to
UCLA to learn about renal transplantation and to export knowledge and skills to Germany. I soon realized, however, that my main interest was prostate cancer. I think one of the reasons was that Dr. Elmer Belt, the uncle of Dr. Willard Goodwin, was one of the staff members of the Department at that time. He was the man who introduced a new technique of total perineal prostatectomy for prostate cancer in the United States and was practicing this technique at UCLA-affiliated hospitals. He was very influential. He actually had me follow up his cases and put them in a database. We did papers together. I wrote some of his presentations. This is how I got involved with prostate cancer.

I became fascinated by some of the issues around prostate cancer; mainly the issue of why some cancers are androgen dependent and others are not. Others start out being androgen dependent and later on they stop being dependent and progress under endocrine treatment. This was fascinating to me. After I finished my 2.5 years of training at UCLA, I was looking around for a year of research and found a position in the laboratory of Dr. Gordon Sato at UCSD. He was a tissue culture man, and the first person to show that functional properties of organ-derived tissues could be preserved in cell cultures.

I worked for him for a year and became very much involved with cell culture and the development of models for human prostate cancer.

This all resulted in a continuous line of research. When I returned to Germany I obtained a grant from the German
Research Association that was extended every time I asked for an extension. I had Japanese fellows and Americans working with me. We followed up on the idea of developing models for prostate cancer. Around that time, when I returned in the early 1970s, the nude mouse became a common model to study trans- planted human cancer tissues.

We were the first ones to show that prostate cancer could grow in nude mice. After I moved to the Academic hospital of Erasmus University in Rotterdam, The Netherlands, we developed 13 permanent lines of prostate and renal cancer all with different characteristics in the nude mouse. They are still available in our center and in other centers for use in research and for commercial purposes like drug testing. I must say I am very proud of these achievements. I have been retired for twelve years, but the lines are still in use and are very prominent in the Department.

You recently published the 13-year results from the European Randomized Study of Prostate Cancer, or ERSPC (see http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60525-0/abstract). Can you tell my readers a little bit about the study design, its endpoints, and a summary of its 9, 11, and 13 year results.

We had Dr. William Catalona in Rotterdam as our visiting professor in 1990, one year before he published his keynote paper in the New England Journal Of Medicine on the value of PSA for early detection of prostate cancer as shown in his St. Louis, MO screening project. We had the advantage in that by 1990 he was already showing us the data. I was fascinated by
this and immediately thought about starting a randomized screening study.

After conducting pilot studies, in 1994 we built a European coalition to evaluate prostate cancer screening in a randomized multicenter setting. We randomized patients blindly to a screening versus control group. The protocol we designed had the main endpoint of prostate cancer mortality. As some people comment, we did not use overall mortality or all-cause mortality. As you look at screening and the development of screening for cancer in general, you won't find a single study or introduced screening policy that addresses all-cause mortality, because that would require 1,000,000 participants-more than we could recruit. Our study didn't have the power needed and we didn't intend to study all-cause mortality.

We decided within the centers that there should be a certain freedom: every center could structure its own study within agreed limits. We also designed a common database, which every-body had to follow. We agreed on the age group of 50-74 and an age group to which everybody had to randomize of 55 to 69. We called that the core age group. That core age group was the one discussed in our most recent publication. It has 162,388 men randomized between screen and control groups.

We also agreed on a screening interval of 4 years with one exception: Sweden insisted on a 2-year interval. Why did we choose a 4-year interval? In the 1990s, we had very little information on the lead-time produced by screening. There
was a paper by Dr. Gann that told us that the lead-time would be somewhere between 5 and 10 years, so we chose 4 years. The Swedes were somewhat more cautious and chose 2 years. We also agreed, as was common during that period of time, on the use of sextant, and later on lateral sextant biopsies, meaning that we did six biopsies per prostate independent of prostate size.

The PSA cutoff we used for biopsy was 3.0 nanogram/mL, which is 1.0 nanogram point lower than the commonly used 4 nanogram/mL, which was also used in Dr. Catalona's study. We were happy with this decision, because we think that in the PSA range of 3.0-4.0, we find a lot of important information and important cancers. I'm sorry to say that some of our centers, specifically Finland, found this cutoff too low and insisted that they would use rectal examination or a free total PSA ratio for the PSA range 3.0 to 4.0. The gross majority of the participants screened with biopsy had a PSA above 3.0 nanogram/mL. The details are listed in Table 1 of the paper.

Our study has an 80% percent power to show a 25% difference in prostate cancer mortality. We have published this power calculation in 2003 in the *British Journal of Urology*, Supplement.

We have, as I mentioned, an 80% power to show a 25% difference at 10 years. To our great surprise, our independent and blinded data committee reported a significant difference in 2008 with an 8-year follow-up. We decided to publish the results in the *New England Journal of Medicine* in 2009.

We now have an added total period of 4 years after the first
publication. We published that data in *The Lancet* in August 2014. The publication provides an update with a median and average follow up of 13 years. Let me add one other thing that may be more related to the methodology.

We have used in line with changing rules and strategies of reporting this type of data to truncate the data. We omitted the data available beyond the 13-year cutoff point. That is different from what we reported previously and it has an impact on the outcomes. You can see that by looking at the paper, which reports for the first evaluation from the 8-year data a rate ratio of 85%. That's a 15% risk reduction; it contradicts the 20% risk reduction in our first paper. This difference is due to a different way of analyzing the study. Which is correct? I don't know. We'll just have to wait for more data.

The main finding we have now is that the rate ratio of prostate cancer mortality between the screen and control arm is 0.79; that translates into a relative risk reduction of prostate cancer mortality of 21% for those who are screened in comparison to those who are not in the control arm.

Sadly, some men get randomized, but don't show up because they change their mind on the way. If we test for that by excluding them from the analysis, then the risk reduction of prostate cancer mortality goes to 27% instead of 21%. This is the figure that can be related to men who wish to be screened. Another adjustment would need to be made and that is to correct for the PSA use in the control arm. Our data on that is still being corrected. They are incomplete at present; therefore,
this correction is not included. We can, however, expect that this will lead to another net increase of the rate of risk reduction.

There is another important measure and that is the absolute risk reduction of prostate cancer mortality. That is not related to the control arm, but to the overall chance of dying of prostate cancer. The absolute risk reduction can be measured and expressed in a different way. The common way to look at it is to look at the number of men we need to screen to avoid one prostate cancer death. This number is 781; it was 1,410 in our first publication. Then, there is the number we need to treat to avoid one prostate cancer death, which is the same as the number needed to diagnose to avoid one death; we assume that all of those diagnosed are also treated. That number is now 27. It was 48.

The numbers needed to screen and the numbers needed to treat bring us very close to the 13-year follow-up results of breast cancer screening studies. If the tendency we're seeing of further decrease continues it is a very positive sign and a very positive outcome of our study.

You said you were surprised that there was a significant mortality reduction in Sweden and in the Netherlands, but not in Finland. Can you talk a little bit about that?

There's a table in the paper giving the results. I think it is in the appendix. There, you can see that the only two centers that show a significant difference are those in Sweden and in the Netherlands. The question is why would that be? There are a number of major differences. The Finnish group has decided
to screen only 3 times. The screening in the Netherlands has been continuous. Screening in Sweden has also been continuous—though every 2 years.

We now believe that screening has to be continuous. This is subject to further analysis, which we will probably publish within one year. We will compare the different effects of discontinued versus continuous screening on mortality.

Also, a number of centers have decided early on, as I already mentioned, that the cutoff PSA of 3.0 was a very low. That turns out to be very important now. They have used ancillary tests in the PSA range of 3.0 to 4.0, such as rectal examination or free total ratio of PSA. That has also happened in Finland.

If you look at Table 1 in the paper, you'll see that for Finland the proportion of biopsy indications followed by biopsy is very high. It is above 80%. The proportion of positive tests is rather low. That is probably caused by the way the Finnish group dealt with the PSA range of 3.0 to 4.0.

These are the major differences I can see at the moment. Other potential differences could come from the underlying incidence and underlying mortality, which varies grossly between Northern and Southern European countries by about 25-30%. As I said, and I once again say, it is subject to investigation at the moment. It is in the hands of my successor professor Hugosson, as the chair of the ERSPC. He will probably be lead also on this paper.

*What are the study’s implications for the global screening debate?*
There is a definite benefit to screening; it reduces prostate cancer mortality. The question is whether in a model analysis of benefits versus harms in quality of life adjusted life years it has that benefit. That is, at this moment still doubtful, as we have also published recently in the New England Journal of Medicine.

The main harm of screening is the problem of over-diagnosis. If you look at the incidence data, you'll see that there is a 56% higher incidence of prostate cancer in the screening arm than in the control arm.

Obviously, some of these cases will still progress, be treated and then disappear from the group of the screening arm that they are in now. The data will change with continuous screening, but the proportion of over-diagnosis—which is estimated in our paper to be around 40%-is obviously the biggest part of that excess incidence, as it is called, in the screening arm. This is the major problem, at this moment recognized in most of the guidelines around the world. It's also the reason why our own research group had put in two places in the paper and the conclusion that we do not recommend the introduction of screening at the moment. The over-diagnosis problem needs to be resolved first. The question is, how should the practicing urologists and GPs deal with this situation, and how should patients deal with this situation? The answer to that is informed decision should be applied.

Now, what is that? We have designed an instrument that is available on the website of the Australian prostate cancer
movement movember.com (http://us.movember.com/report-cards/view/id/2385) and also on the website of the SocieteInternationale'd'Urologie (http://www.siu-urology.org). Informed decision-making tools like that one should be used to answer questions that come up when patients ask what the advantages and disadvantages are to having a PSA test. The answer to these questions comes from well-designed, informed decision-making aides.

The other issue that needs to be tackled is what can we do to selectively detect aggressive cancers and exclude them from diagnosis and possibly even from biopsies.

*I spoke a while back with Dr. Lawrence Klotz from Toronto. He said the problem is not with over-diagnosis per se, but rather with overtreatment. Using MRI might help sort out which cancers are aggressive and need to be treated immediately and which are not aggressive and are perhaps eligible for an active surveillance program.*

I think along the same lines as Dr. Klotz about the selective detection of aggressive cancers by MRI.

*Do you think that using MRI routinely would that be a wise approach?*

I want to be a little cautious: a definitive answer about MRI's use is not in yet. This is also the reason why Dr. Klotz and our own group have agreed to participate in a worldwide study initiated from the Royal Marsden Hospital in London (http://www.royalmarsden.nhs.uk).
We need studies in a multicenter setting, because the application of MRI by a radiologist is difficult. Radiologists have to go through a learning process. We understand that not every radiologist is ready to learn how to perform a good prostate MRI and a good analysis of that MRI.

We don't have multicenter information.

We don't have comparative information that is truly valid. There are some smaller studies, but there are a number of very important unanswered questions that need to be addressed.

I am a co-author of a recent study published by a group from Brisbane. We looked at 223 clinical cases. It has the same problems shown by other MRI studies: you classify tumors as being Grade 1, 2 or 3, but if you do ultrasound-guided biopsies you still encounter somewhere between 25-30% percent of aggressive cancers that the MRI doesn't identify.

I think one of the best studies so far is the study from the NCI in the United States by Dr. Siddiqi (www.sciencedirect.com/science/article/pii/S0302283813005988). That paper anticipates that in the future, not only MRI-guided, but MRI and TRUS-guided biopsies will be needed. We miss too many aggressive cancers with the MRI-guided biopsies in the range of favorable PI-RADS.

I also spoke a few months back with Drs. Matthew Cooperberg and Peter Carroll from UCSF about other risk assessment tools like CAPRA and genetic tests like Decipher and Prolaris.
What do you think about using those tools as a method of sorting out aggressive from non-aggressive cancers?

I think they're excellent tools. We also have our own risk calculator, which is at http://www.prostatecancer-riskcalculator.com. It's a validated instrument. All of these instruments, including the instrument developed in San Francisco, are valid, but they all have one disadvantage (including our own). You first have to have a biopsy.

What the MRI promises is that we can avoid biopsies in a large group of men. That makes a big difference to all of the other regimens that are proposed for risk ratification. They are all post-biopsy. The MRI is pre-biopsy.

Are there competitive scans to the MRI, or is the MRI the best technology we have?

It's the best technology we have.

Why do you think is there so much resistance to screening in the United States?

They were screening too much in the United States before the Preventive Services Task Force recommended against routine screening in 2013. That recommendation has decreased screening. I don't agree with everything the statement says, but I think the effect it had in the United States makes a lot of sense. It led to more informed decision-making. It also had an impact on current guidelines. I was delighted to be the Chair of a discussion of American Urological Association guidelines at the last AUA
meeting in May 2014. I think it's a very positive development. People are more educated. They are more critical and don't just allow a doctor to make a choice for them as the PSA stands. Patients want to have a discussion. They want information. They want to participate in informed decision-making. I think these steps have led to a decrease in PSA testing in the United States, which in my view makes a lot of sense.

*Do you think the real problem was over-detection or over-treatment? Only recently has active surveillance (or watchful waiting or medical management) become accepted.*

Active surveillance and watchful waiting are two very different things. We use watchful waiting in much more advanced prostate cancer. I think that there was simply a mood in the United States that was driven by the notion, “Cancer is cancer, and if I have cancer I need to do something about it.” To bring the idea across that you can have a cancer that may not kill you is an intellectual exercise that has only recently been undertaken. It requires a lot of effort to get this message across.

I also think that the American healthcare system is very much driven by money. That may have played a role. It is unlikely that radiotherapists, radiologists, or urologists will influence a person who has prostate cancer to not have the treatment considered standard in the United States-i.e. radical prostatectomy.
Do you think fear of liability played a role?

Yes.

Let's talk about the ARTS trial, which reported last year. That study (http://www.ncbi.nlm.nih.gov/pubmed/23176897) looked at Avodart (dutas-teride) use in men whose PSA is rising after treatment. What are the implications of your results for prostate cancer patients?

ARTS was designed before the FDA did not approve Avodart and Finasteride as preventive agents. I'm very happy that the trial took place. It addresses an issue that was, in my view, debatable about the FDA's decision and the advice given by some of my colleagues, including my friend Dr. Patrick Walsh of Johns Hopkins University.

I believe that the observation that a relatively small group (29 cases) of men on Avodart were shown to develop aggressive cancers—more than in the control arm—is something that could be explained and has been explained as an artifact by several investigators.

One of the main reasons is that if you shrink the prostate by 40-50%, as Avodart does, then you have a much greater chance of detecting a small, poorly differentiated tumor. All of these open questions were not dealt with properly, in my opinion, in the FDA process. They didn't really insist on having the proper data.

In the ARTS trial, we used an approach called tertiary prevention in men with minimal disease. Minimal disease in
that setting is characterized as having a rising PSA as the only marker of progression after radical prostatectomy or radiotherapy. In this setting of tertiary prevention of minimal dis-ease, we used the speed at which the PSA rises as the only parameter that we based our calculations on. We added additional parameters, such as progression of the tumor, the occurrence of progressive lesions, and so on as secondary end points.

The main finding is that in this setting, the time to PSA doubling is significantly reduced by Dutasteride use—that is a stable finding which is still improving after a period of two years. (The trial is limited to two years, unfortunately.) This finding, together with the fact that we did not see any increase of progressive lesions between the screen and control setting, is a contradiction in a way to the notion of the dutasteride and finasteride studies that they might promote progressive aggressive lesions. In my view, that is probably not true. I would say, “Okay, FDA, go back and reconsider your judgment,” but that is not going to happen.

The financial interests of the companies are gone and the patents run out. I am convinced that many of my colleagues are still using Avodart as a preventive agent.

_Do you think it's reasonable to use Avodart in men who have had surgery or radiation as a means of preventing recurrence?_

Yes, I think it is reasonable to do that.

_What do you think are the characteristics of the patients_
most likely to benefit from the use of Avodart after surgery or radiation?

The population that we address in the study is obviously the population most likely to benefit. Since we are addressing and showing that disease progression decreases, then I think that using Avodart in a watchful waiting and active surveillance setting is very sensible, as long as the patient remains under solid urological control—i.e. PSA tests and rectal examinations twice per year. Once that is done, I think we have enough data to safely use this drug in tertiary prevention settings and in men who don't have clinical evidence of prostate cancer, but who want to prevent it from developing

*The side effects from Avodart are really very minor are they not?*

They are very minor. We couldn't find any difference in the well-known and previously described side effects between the screen and control group.

*You said you use Avodart over Proscar because there is a more pronounced decrease of the 5-Alpha DHT. Can you talk a little more about that?*

5-Alpha dihydrotestosterone is the main androgen that promotes the growth of the prostate cancer cell. The level of 5-Alpha dihydrotestosterone in the prostate decreases more with Avodart use than with finasteride use. The simultaneous rise of testosterone has been heavily debated and seems to be less important than the decrease of 5-Alpha dihydrotestosterone, because testosterone's effects on the
prostate cancer cell is about eight to ten times less than 5-
Alpha dihydrotestosterone's effect.