

Prevention Strategies: Emerging Trends and Issues

Daniel Shevrin, MD

Northshore University Healthsystem

I. Rationale for Prevention

Prostate cancer is a significant public health risk, and in autopsy studies 64% of men age 70-80 have histologic evidence of prostate cancer, which is quite amazing. Obviously, not that many men have clinical disease, and it goes completely unnoticed, which has a lot of ramifications with regard to screening. Current screening although it may in fact reduce mortality is not optimal. Prostate cancer has a long natural history for the most part, and epidemiologic studies do suggest dietary risks. Finally, the tumor is clearly under hormonal influence.

II. Challenges of Prevention

The challenges are great. The intervention must be effective. It has to have acceptable toxicity, and the biggest challenge is identifying the population that is at increased risk.

III. Primary Chemotherapy Studies of Prostate Cancer

There are four large studies that have tried to look at some way to prevent prostate cancer.

1. PCPT

The Prostate Cancer Prevention Trial (PCPT) utilized finasteride, which is a 5 alpha-reductase inhibitor, and that showed an almost 25% reduction in the risk of prostate cancer, which was highly statistically significant.

However, the PCPT has become a very controversial study. Approximately 19,000 men were randomized at over 200 sites. They had to be 55 or older with a normal DRE, a PSA less than three and no BPH. For-cause biopsies were done when PSAs went up above four or there was an abnormal DRE. If the patients didn't do so, at the end of seven years, patients were to have a mandatory biopsy. When you added up the for-cause biopsies and those done at the end of seven years, there was an approximately 25% reduction in the number of prostate cancers in the finasteride group compared to the placebo group.

The controversial issues that have surrounded PCPT are the for-cause biopsies, the fact that there were fewer for-cause biopsies with finasteride, there are more high-grade tumors with finasteride and finasteride lowers PSA by about 50% so it may provide a false sense of security.

The conclusions that can be drawn from the PCPT study are that finasteride use was associated with mild sexual side effects. Finasteride reduced the size of the prostate and improved urinary symptoms. Men who were treated with finasteride had 24.8% fewer prostate cancers, and men treated with finasteride had a 27% increase in high-grade prostate cancer. Does finasteride simply make it easier to detect high-grade tumors by reducing the size of the prostate? Does finasteride simply delay the

progression of low-grade tumors and cannot control the high-grade? This is one fear, and the other fear is that the use of finasteride in some way may even cause some of the high-grade tumors. These things remain controversial, and there is no sure answer.

2. SELECT

The SELECT trial utilized selenium and vitamin E, which targeted oxidative stress, and it was reported in 2009 that there was absolutely no benefit.

This study randomized 35,533 men, 50+ African American men and 55+ Caucasian men with a PSA of less than four and no cancer. There were four groups: selenium, vitamin E, both or neither. The annual DRE and/or PSA were done according to the study sites' standards of care and patient preference. Again, there was no decrease in the risk of prostate cancer with either selenium, vitamin E or both. In fact, there was a slightly increased risk for prostate cancer with vitamin E, which is a little bit of a cautionary note.

3. Physicians' Health Study II

The Physicians' Health Study II utilized vitamins E and C and targeted oxidative stress, and no benefit was reported.

4. REDUCE

Finally, a study that is ongoing is Reduction by Dutasteride Prostate Cancer Events (REDUCE). The agent being utilized is dutasteride, which is again a 5 alpha-reductase inhibitor, and the updated results show an almost 23% reduction in the risk of prostate cancer.

REDUCE is a randomized, placebo-controlled trial sponsored by GSK of 8,231 patients with single-negative prostate biopsy. The use of dutasteride decreased the rate of prostate cancer by 23%. Most cancers were detected on a scheduled biopsy. The reduction was mostly in low-grade cancers, and dutasteride did not increase the detection of high-grade prostate cancer. Were men in this trial at lower risk for prostate cancer due to the previous negative biopsy? Does this simply represent the prevention of a new cancer or inhibition of an existing cancer?

IV. Current Recommendation on Use of 5-ARIs

The American Society of Clinical Oncology and the American Urological Association issued the 2008 Clinical Practice Guideline, in which they concluded, "Asymptomatic men with a prostate-specific antigen (PSA) of less than or equal to 3.0 ng/mL who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of both the benefits of 5-ARIs for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer)."

V. Statins as Chemoprevention of Prostate Cancer

There is a basic science foundation for how statins can have an inhibitory effect on prostate cancer. There is the inhibition of "lipid rafts" in cell membranes, the possible inhibitor of tissue testosterone levels, the reduction of cholesterol precursors, and the possible direct apoptotic, antiangiogenic and anti-inflammatory effects.

Two large epidemiologic studies have shown a 50-60% reduction in overall prostate cancer risk among statin users. Three meta-analyses on the other hand showed no association between statin use and overall prostate cancer. It may be that where we will see some benefit is in the reduction of advanced prostate cancer. We know that statins can actually lower PSA at diagnosis, but it may be that what we are seeing is a possible detection bias as statin users are more likely to undergo PSA screening. Statins may actually augment or help other therapies including radiation therapy and radical prostatectomy.

VI. Chemoprevention: Where are we?

Nutritional prevention studies have been negative, which was a big disappointment, and 5 alpha-reductase inhibitors reduce risk. That being said, the degree of reduction remains controversial. The reason for the increased risk of high-grade tumors remains unknown, and in fact very few physicians are changing their practice. Statins are still very interesting in terms of whether they may have some role to play, but developing a trial is very challenging. In many ways, we are back to the drawing board.

Diet may have some impact, but we don't know for certain what the right diet is. There is evidence to say that a diet that is good for the heart is good for the prostate. It probably will have some effect on reducing the risk, but we don't know for sure. As far as true chemoprevention, unfortunately right now we don't have anything solid. There is, however, a lot of research that is ongoing in this area.