Proscar® Reduced Incidence of Prostate Cancer 25%

PCRI is honored to publish our first article from Paul Schellhammer, MD. His perspective is even richer because he is a prostate cancer survivor himself. After medical training, he joined the practice of Devine Poutasse Fiveash and served as Chairman of the Department of Urology and Program Director of the Resident Training Program at Eastern Virginia Medical School. Dr. Schellhammer has made many contributions to the field of urologic oncology and published widely in that discipline, especially in prostate cancer. He serves on several editorial boards, and has served as a trustee of the American Board of Urology as its President. He has also served as President of the Society of Urologic Oncology, as President of his Mid-Atlantic Section of the American Urologic Association, as a member of the Board of Directors of the American Urologic Association, and President of the American Urologic Association 2007-2008

Chemoprevention *of* Prostate Cancer

Proscar® and Avodart® Proven Effective

What are the risks?

Paul Schellhammer, M.D.

Strategies to prevent onset or occurrence of cancer are certainly attractive and the concept dates back to our country's forefather, Benjamin Franklin, whose aphorism – "an ounce of prevention is worth a pound of cure" has withstood the test of time. The major challenge of a chemopreventive agent is as follows: it must be virtually side-effect free as it will be applied in a well, healthy population, at risk for, but not suffering from the disease in question. Hippocrates' admonition of "first do no harm" clearly applies to any chemoprevention strategy. Prostate cancer represents an important target for chemoprevention based on the fact that it is a common disease found with increasing frequency in the aging male. Any effort that prevents disease, or even delays progression of disease (chemo suppression or chemo retardation may be more appropriate terms), will realize the important outcome of avoiding a prostate cancer diagnosis and its treatment side-effect within the lifetime of the an individual.

The Prostate Cancer Prevention Trial (1), the results of which were published in the *New England Journal of Medicine* in 2003 studied finasteride (Proscar®), a 5-alpha reductase inhibitor, for its ability to the reduce the incidence or period prevalence of prostate cancer over the seven year time frame of the study. I recall when the trial was in development, comments to the affect that it would be an important trial not only to determine the chemopreventive effect of finasteride, but also to study the drug in a large, well-controlled population. As finasteride had just recently been approved by the FDA for the treatment of urinary obstructive symptoms, it was anticipated that it would be administered to a large segment of the aging US male population, and more information with regard to its effect on cancer as well as obstructive symptoms was deemed very important.

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COMPARISON OF TRIALS IN PC PREVENTION

		PCPT Trial (finasteride/ Proscar)	REDUCE Trial (dutasteride / Avodart)
Men studied	Age at entry	Over 55	50 - 75
	PSA at entry	3.0 or less	2.5 to 10.0
	DRE at entry	Normal required	Normal not required
	Biopsy history at entry	None required	Previous negative biopsy required
Study design	# of men in study	18,882	6,729
	# of years study conducted	7	4
	Placebo arm?	Yes	Yes
Results	Urinary symptoms improved?	Yes	Yes
	Reduction in pre-cancerous cells at biopsy (HGPIN and/ or ASAP)?	Yes	Yes
	Rate of PC prevention	24.8%	22.8%
Published		*NEJM July 2003*	*NEJM April 2010*

The Prostate Cancer Prevention Trial (PCPT) was halted early when it was determined by the monitoring committee that a significant reduction in prostate cancer incidence was achieved in the finasteride arm of the study. The absolute reduction in prostate cancer incidence was six percent which represented 25% relative decrease in the incidence of prostate cancer in the treatment versus the control arm. What was also reported, and what received much greater attention, was the apparent increase in high grade cancer amongst men receiving finasteride. Over the ensuing five years, an extensive study of the dataset provided a number of very logical explanations as to why this initial finding occurred, and demonstrated that with appropriate adjustments the increase in high grade was not authentic. While never verifiable with absolute 100% certainty, it was verifiable beyond reasonable doubt that finasteride did not cause higher grade disease.

Avodart reduced incidence of prostate cancer 22%. In April 2010, the New England Journal of Medicine, published the reports of a second chemopreventive trial, Reduction by Dutasteride of Prostate Cancer Events (REDUCE), which addressed the issue of prostate cancer diagnosis in a different population using another 5-alpha reductase inhibitor, dutasteride (Avodart®). In addition to blocking the Type II receptor for converting testosterone to the more potent dihydrotestosterone and therefore similar to finasteride, dutasteride also blocked a second pathway mediated by the Type I receptor. It is therefore termed a "dual 5-ARI inhibitor" with anticipated greater efficacy as a result. While the PCPT trial enrolled any male greater than the age of 55 with a PSA of less than 3, the REDUCE

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trial focused on a group of men with a PSA between 2.5 and 10, who had, within the most recent six months, a biopsy negative for prostate cancer. Approximately 4,000 men were enrolled in each arm. All men were scheduled for a prostate biopsy at 2 and 4 years following randomization. At both year 2 and 4, the biopsy incidence of prostate cancer was reduced by 22%. This reduction paralleled the reduction that had been reported in the PCPT trial. In the REDUCE trial, there was no overall increase of high-grade cancer among patients receiving dutasteride, although in the four year arm there were more high grade tumors in the cohort of men receiving dutasteride. Very reasonable explanations for this finding at the 4 year mark have been put forward. In addition, like the Prostate Cancer Prevention Trial, men receiving 5-alpha reductase inhibitor had a lower incidence of high grade PIN (prostatic intraepithelial neoplasia) and in the REDUCE trial, a lower incidence also of ASAP (atypical small acinar proliferation). Both ASAP and high grade PIN are considered to be pre-cancerous or precursors of prostate cancer.

Avodart and Heart Failure. One unusual finding with the REDUCE trial was the increased number of patients on the treatment arm who evidenced congestive heart failure. The number of events were extraordinarily low (30 of 3305 in the treatment arm in 16 of 3424 in the placebo arm). There was concomitant use of alpha blockers (such as Flomax®, Cardura®, or Hytrin®) in these patients and this may have contributed to the difference. Of importance is that in over 10 years of research on thousands of men, no other clinical trial conducted with 5-alpha reductase inhibitors for patients with urinary symptoms, ever demonstrated this finding (2,3,4). However, Avodart should be withheld or used with caution in men with signs and symptoms of congestive heart failure until further information is available. Finally, in both PCPT and REDUCE, urinary symptomatology, the incidence of urinary retention, and surgery for obstructive symptoms were all reduced.

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Level I evidence is the term used to describe outcomes that derived from large, well constructed randomized controlled trials (RCT). Level I evidence is reinforced when more than one large RCT reaches the same conclusion. Level I evidence provided by these trials constitute the foundation for evidence-based medicine. Urologists and patients (men) have two very powerful trials to support prostate cancer prevention. The 2009 AUA / ASCO guideline and responses to frequently asked questions about chemoprevention are available on the ASCO website (5). This information will be of great help to the patient in making a decision to pursue prostate cancer prevention. I believe that programs to promote screening / early detection should be coupled to a strategy of chemo prevention. If the frequency of prostate cancer diagnosis can be reduced within the lifetime of the individual, then more research and resources can be directed towards those cancers which are not prevented and which are more likely to be a threat to duration and quality of life.

GLOSSARY:

Chemoprevention - The use of chemical agents, drugs, or food supplements to prevent disease. http://medical-dictionary.thefreedictionary.com/chemoprevention

5-alpha reductase inhibitor: A drug used to treat urinary symptoms due to enlarged prostate (BPH) by blocking the conversion of testosterone to dihydrotestosterone. Currently available: finasteride (Proscar®) and dutasteride (Avodart®).

Heart failure – In context of the REDUCE study, this means congestive heart failure (a treatable and reversible condition), – it does not imply stopping of one's heart.

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