A few years ago, I attended the annual meeting of the Clinical Ligand Assay Society. From the airport, I took a taxi to my hotel. The taxi driver, a 60-year-old man, was curious and asked why I was visiting Philadelphia. I told him that I was attending a medical conference and giving a lecture on prostate cancer. He immediately got very excited! He showed me a 2-L Coca Cola® bottle, which was half full with a reddish fluid. He then asked me, “Do you know what this is?” I told him that I had never seen red Coca Cola and I wondered if it was a new product. He laughed and told me that only the bottle was from Coca Cola and that the content was watermelon juice. He mentioned drinking approximately 2 L per day, and when I asked why, he explained that somebody told him that drinking 2 L of watermelon juice per day could prevent the development of prostate cancer. He then told me that his PSA (prostate-specific antigen) was going down, and I was admittedly a bit ashamed that I did not know about this “new” chemopreventive agent. I used the story as an introduction to my lecture, and it seemed to have worked well with the audience.

It is now 10 years later, and I am reviewing the recent literature on chemoprevention of prostate cancer with a new agent, dutasteride (1). This is not the first time that a chemical agent has been tried for prostate cancer prevention. The Prostate Cancer Prevention Trial (PCPT) tested finasteride with some apparently promising results (2) (see also below), and a Finnish study also examined finasteride (3). On the basis of these and other data, the American Society of Clinical Oncology and the American Urological Association issued a guideline recommending consideration of such agents for prostate cancer chemoprevention (4).

But let me take a step back first. Not all diseases are amenable to effective prevention, but prostate cancer is an ideal candidate. It has a high prevalence, is potentially lethal, and poses a huge burden on the healthcare system because of the costs associated with its diagnosis and therapy. Because the disease usually progresses relatively slowly, prevention or further slowing of its progression would help millions of men worldwide and save many resources. Even halving the number of prostate biopsies, currently at approximately $1 \times 10^6$/year in the US alone, could save hundreds of millions of dollars.

Androgens are well known to be implicated in prostate cancer initiation and progression. The biologically active androgen dihydrotestosterone is produced from testosterone in the prostate by the action of type 1 and type 2 steroid 5α-reductase isoenzymes. Finasteride is an inhibitor of the type 1 isoenzyme, and dutasteride, a newer agent, inhibits both isoenzymes. It is important to first examine what happened with the finasteride chemoprevention trials.

I caution that the issue under discussion seems initially straightforward, suggesting that a well-designed, blinded, placebo-controlled prospective clinical trial would provide the answer. But things are not as simple as they look. In the PCPT (2), almost 19,000 participants were given 5 mg/day of finasteride or placebo and then monitored for 7 years. The primary end point was the prevalence of prostate cancer over the 7 years, confirmed either during or at the end of the period with a prostatic biopsy. This study found prostate cancer in 18.4% of the participants in the finasteride group and 26.4% of the placebo group, which translates to a 6% absolute reduction and a 25% relative reduction. This reduction, however, came at a cost and with an added bonus. The cost was that the proportion of high-grade tumors (Gleason score, 7–10) in the finasteride group was higher than in the control group ($P < 0.001$) and that the sexual side effects were more common in the finasteride group. A few years later, the former finding was attributed to a bias in the trial design, and recalculation showed that the effect was no longer significant. The added bonus was that the frequency of urinary symptoms (such as acute urinary retention) in the finasteride group was lower than in the placebo group. The Finnish study (3) found no difference in prostate cancer incidence between the finasteride and placebo groups.

In the recent dutasteride study (1), approximately 7000 men were randomized to receive either 0.5 mg
dutasteride daily or placebo for 4 years, with biopsies obtained before the trial and at 2 and 4 years. This study found a prostate cancer incidence of 19.9% in the dutasteride group and 25.1% in the control group, for an absolute decrease of 5.2% and a relative decrease of 23%. The apparent decrease also came with some unfavorable side effects and a bonus, however. The side effects included a statistically significant loss of or decrease in libido, erectile dysfunction, decreased semen volume, and gynecomastia, in addition to an unexpected increase in cardiac failure events. Moreover, the dutasteride group had 12 times more tumors of Gleason grade 8–10 in years 3 and 4, but not in years 1 and 2, a finding pointing to the possibility that longer exposure to the drug may lead to high-grade, and potentially lethal, tumors. The bonus was the same as in the finasteride study, namely a reduction in acute urinary retention events.

What do these data mean? In an insightful editorial, Patrick C. Walsh raised a few important issues that complicate the interpretation of these seemingly straightforward data (5).

First, it is unequivocally accepted that finasteride and dutasteride shrink the prostate gland dramatically and reduce the serum PSA concentration by >50%. In the study under discussion (1), patients were scheduled to have biopsies at 2 and 4 years; however, this is not the usual setting for a prevention strategy. In a real-world scenario, individuals will be given the agent and then monitored; only when there is indication of malignancy would a biopsy be performed. Indications for biopsy would include an increasing PSA value or an abnormal result in the digital rectal examination. It is not clear how the data of the report under discussion (1) would play out at the end, given that both finasteride and dutasteride clearly would reduce the serum PSA concentration, possibly giving a false impression of security in these patients. It is not clear how the shrunken prostate would affect biopsy results (possibly making it easier to detect a cancer, thereby introducing a bias) and how the drug would affect small and benign indolent tumors in the long run, in that the drug might trigger such tumors to develop into more aggressive ones. In the PCPT trial, patients were given a biopsy when they had an increasing PSA value or an abnormal result in the digital rectal examination, so when one considers only the patients who actually underwent a biopsy, the effect of finasteride was smaller (10% reduction, not statistically significant) (5).

Another issue with the report under discussion (1) is that dutasteride likely decreased the incidence of tumors of Gleason grades 5 and 6, not tumors with higher Gleason scores, which are the lethal ones and should be the ones to target for prevention.

How can the available data on this subject be summarized? Unequivocally, dutasteride and finasteride reduce prostate volume and serum PSA and help with the urinary tract symptoms of benign prostatic hyperplasia. The beneficial effects on urinary symptoms come at the price of some side effects, such as sexual dysfunction. The lowering of the serum PSA concentration should be interpreted with great caution because it may give the false impression of PSA being “normal” under the influence of these drugs. In patients receiving the drugs, an increasing PSA value, even within the reference interval, may be highly suspicious for malignancy. It is not clear whether there is a benefit of these chemoprevention modalities for prostate cancer, especially for high-grade, lethal tumors.

Last but not least, I comment on what an effective prevention agent should be able to do. A good benchmark is vaccines, which are very effective at preventing infectious diseases with minimal or no side effects. The agents tried so far for prostate cancer seem to be minimally effective, if at all, and may carry significant risks and undesirable side effects. 5α-Reductase enzymes may not be good targets for prostate cancer chemoprevention, despite the biologically sound basis for their use. Such considerations do not mean that efforts to prevent this important cancer should cease. We just have to find better targets.

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