



Weill Medical College of Cornell University Reports on Men's Urologic Health

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Benign Prostatic Hyperplasia Disease: Is Prevention Feasible?

By Leonard S. Marks, MD*

If the 20th century was the age of astonishing cures, the 21st may turn out to be the era in which those cures became irrelevant.

—Time magazine cover story, 'Prevention of Disease,' January 21, 2002

Prevention, the most advanced form of disease control, is the ultimate aim of medical science. However, benign prostatic hyperplasia (BPH), which is a progressive disease process, has always been treated late in its course. Throughout

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most of the 20th century, when the pathology of BPH progressed to the stage of BPH disease, the unfortunate men who developed complications were treated after the fact with surgical remedies ('astonishing cures'). Until recently, control of the BPH process was not possible, and prevention was unthinkable. Now, in the 21st century, a safe, well-tolerated way to control the fundamental BPH process, 5 α -reductase inhibition (5ARI), has become available.¹ With 5ARI treatment, prevention of BPH disease appears to be feasible for many men,² offering them the hope that the astonishing cures of the previous century have become, if not irrelevant, only a last resort.

BPH Disease vs BPH Histology

BPH disease is different from BPH histology. Histologic BPH is characterized by an increase in the number of glandular and muscular cells, beginning in the third or fourth decade of life and becoming nearly universal with age. BPH disease, a clinical entity, may be defined as a life-altering

urinary condition caused by bladder outlet obstruction (BOO) due to an enlarged prostate (EP) that requires medical intervention.^{1,2} Viewed in isolation, the histologic changes are of little clinical relevance. However, as prostate growth reaches a volume of approximately 30 cc to 40 cc, the natural history of BPH changes, and BPH disease becomes increasingly likely.^{3,4} BPH disease is clinically recognized by urinary retention, bleeding, infection, bladder stones, irreversible changes in the bladder wall, and lifestyle disruption from intolerable symptoms. BPH disease may be considered the final stage of BPH progression; it was at this late stage that the 'astonishing cures' of the 20th century were applied. Among those 'astonishing cures' was the transurethral prostatectomy (TURP), universally considered one of the great surgical advances of that time and a precursor of modern laparoscopic surgery.

The prevention concept applies not only to fatal diseases, like heart disease, cancer, and stroke, but also to certain nonfatal conditions that severely affect quality of life. In one

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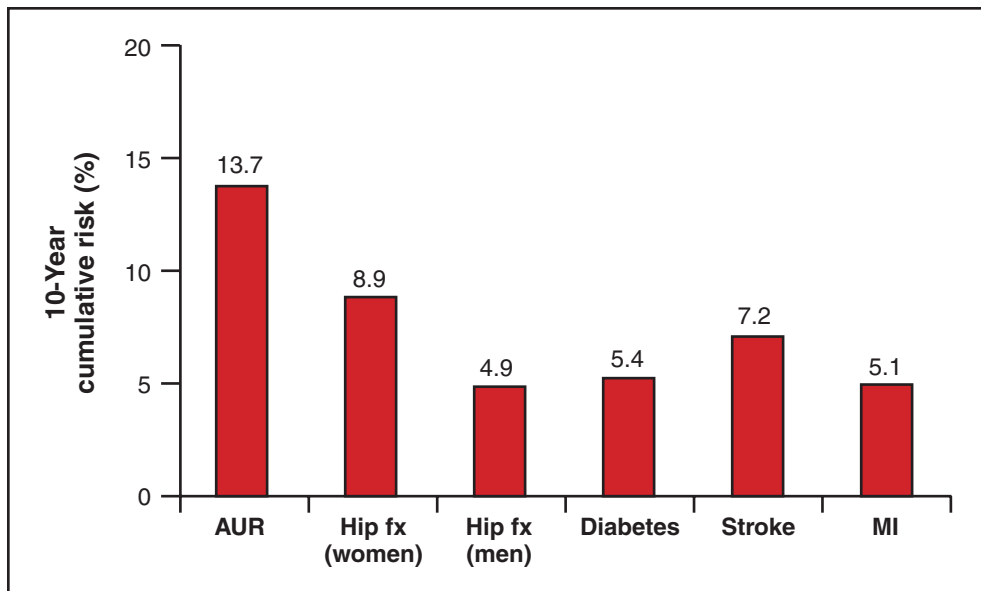


Figure 1: Risk of AUR vs other preventable diseases. Ten-year cumulative risk for AUR in 60-year-old men compared with the risk for other common diseases for which preventive therapy is available. Reprinted with permission from Jacobsen et al.¹⁰

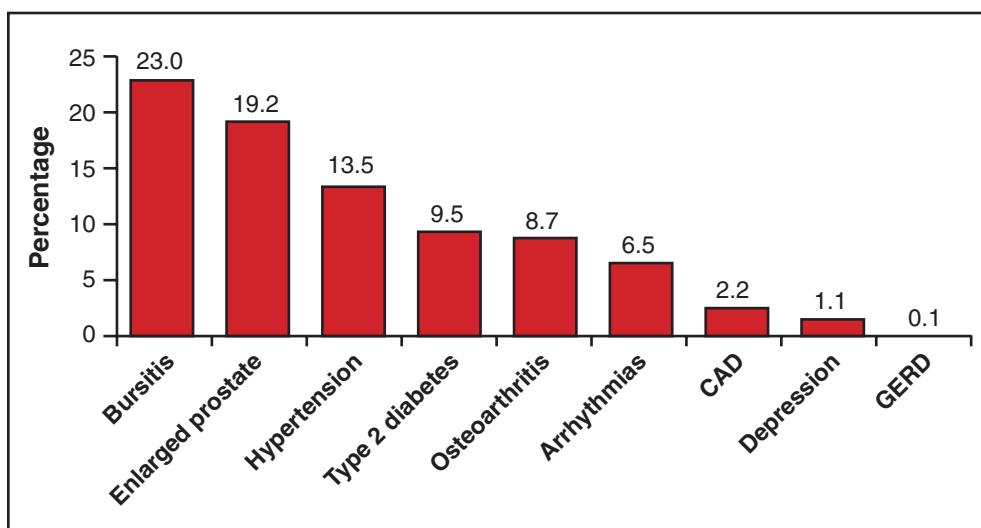


Figure 2: Likelihood of experiencing a significant event (BPH surgery or AUR) within 1 year classified by diagnosis. Reprinted with permission from Fenter et al.¹⁴ CAD=coronary artery disease; GERD=gastroesophageal reflux disease

dramatic example, the prevention of dental caries, the value of water fluoridation is well established and widely recommended.⁵ Every dollar spent on water fluoridation results in approximately \$38 saved in restorative treatment costs, associated with a 30% to 50% reduction in tooth decay, according to the US Centers for Disease Control (CDC).⁶ Another example where intervention for a nonfatal disease can have a dramatic impact on quality of life is preventive treatment for osteoporosis. In a special report on bone health, the US Surgeon General recommended treatment (ie, calcium, vitamin D, bisphosphonates) for all postmenopausal women with low bone density, whether they are symptomatic or not.⁷ Hypertension

can also be considered here, since to a person with asymptomatic blood pressure elevation, no overt sign of illness is present, and he or she feels healthy. Nevertheless, any degree of raised blood pressure is a risk factor for long-term complications, and early, preventive treatment has become the standard of practice.⁸ Similarly, prevention of glaucoma by the routine measurement of intraocular pressure and drug treatment of individuals with elevated pressures, whether symptomatic or not, is now widely accepted.⁹ These examples illustrate that prevention of disease, including major, common nonfatal disease, serves an important public health function, reducing both dollar and human costs.

Risk of BPH Disease

BPH disease is a common occurrence. The most clearly defined end point of BPH progression is acute urinary retention (AUR) because it is easily recognized, uniformly treated, and coded in a standard fashion. In the widely quoted Olmsted County Study (page 3), the 10-year risk of AUR for a 60-year-old man with symptoms of only moderate severity was found to be 13.7%.¹⁰ This risk exceeds the risk of an osteoporotic fracture, a stroke, or a myocardial infarction (Figure 1). By widespread agreement, these latter conditions are all treated in a preventive fashion, even in individuals with few symptoms when the condition is first recognized. Similarly, prevention of BPH disease also merits consideration when a progressive condition is first recognized, regardless of symptom status.¹¹⁻¹³ In recent data from a large Medicare sample, the risk of a man developing AUR or undergoing surgery for BPH within 1 year after recognition of an 'enlarged prostate' was approximately 19% (Figure 2).¹⁴ The risk of BPH disease from an enlarged prostate is a real possibility and should not be ignored, even if the individual has few symptoms of BOO.

DHT Mediates Prostate Growth

BPH disease is mediated from the outset by dihydrotestosterone (DHT), the main stimulant of growth factors within the prostate gland (Figure 3).¹⁵⁻¹⁷ In brief, testosterone enters the prostate via systemic circulation. Within the stromal cells of the gland, testosterone is converted by the 5 α -reductase enzyme (Types 1 and 2) to the active intraprostatic androgen DHT. The DHT binds to the androgen receptors, forming a dimer, which migrates into the nuclei and engages the target genes, resulting in mRNA synthesis. The specific mRNA stimulates the formation of signaling factors, which migrate into adjacent epithelial cells and modulate cell division and growth of the organ. This pathophysiology has been explained in a recent review article and accompanying online video clip.¹⁵

Effects of 5ARI Drugs on the Prostate

The 5ARI drugs finasteride (Proscar®)¹⁸ and dutasteride (Avodart®)¹⁹ interrupt the androgenic pathway in the prostate by blocking the conversion of testosterone to DHT. As a result of this block, the gland is deprived of DHT, the main trophic substance in the prostate, and a process of involution ensues.

When boys are deprived of DHT from birth, the gland does not develop;²⁰ when adult men with symptomatic BPH undergo pharmacologic DHT deprivation, their prostates shrink, symptoms are often relieved, and complications obviated;^{19,21} and theoretically, if the DHT-mediated pathology were to be interrupted early in adult men, BPH disease could likely be prevented.^{1,2} Among the known effects that 5ARI drugs induce in the human prostate are (1) a profound reduction of DHT levels,^{22,23} (2) regression of subendothelial microvessels,²⁴ (3) a trend toward apoptosis,²³ (4) contraction of epithelial cells,^{23,25} and (5) a decrease in gland volume, which is equally distributed between transition and peripheral zones.^{25,26} Importantly, the tissue effects of the 5ARI drugs are not related to voiding symptoms, since even men with few symptoms exhibit the same drug-induced changes as men with advanced symptoms.^{23,25}

Prostate Volume and BPH Natural History

Progression of BPH from histologic curiosity to disease state is determined primarily by prostate volume, the linchpin of this logic.^{3,10} The larger the prostate, the greater the propensity to progress to the complication stage. Among the first to demonstrate this were the Mayo Clinic investigators who studied men living in the surrounding area of Olmsted County, Minnesota. The landmark Olmsted County Project used teams of trained medical personnel who called on randomly selected adult men in their homes, enlisting their cooperation in a longitudinal study of prostate growth and related clinical manifestations.³ Men in this study were not patients in a urology clinic and were otherwise healthy (40 to 70 years) without any overt prostatic diseases. These men were selected on a geographic basis for a longitudinal study of the natural history of prostate growth. Men with prostate volumes exceeding 30 cc were 3 times more likely to develop AUR than men with prostate volumes <30 cc (4-year follow-up).^{3,10} Voiding symptoms, depressed flow, and advanced age were also associated with risk of AUR. However, when Roehrborn et al²⁷ performed a detailed analysis of 110 clinical variables (eg, symptoms, flow, age) in thousands of men in various BPH trials, prostate volume and its surrogate, prostate-specific antigen (PSA), clearly emerged as the single most important predictor of AUR.

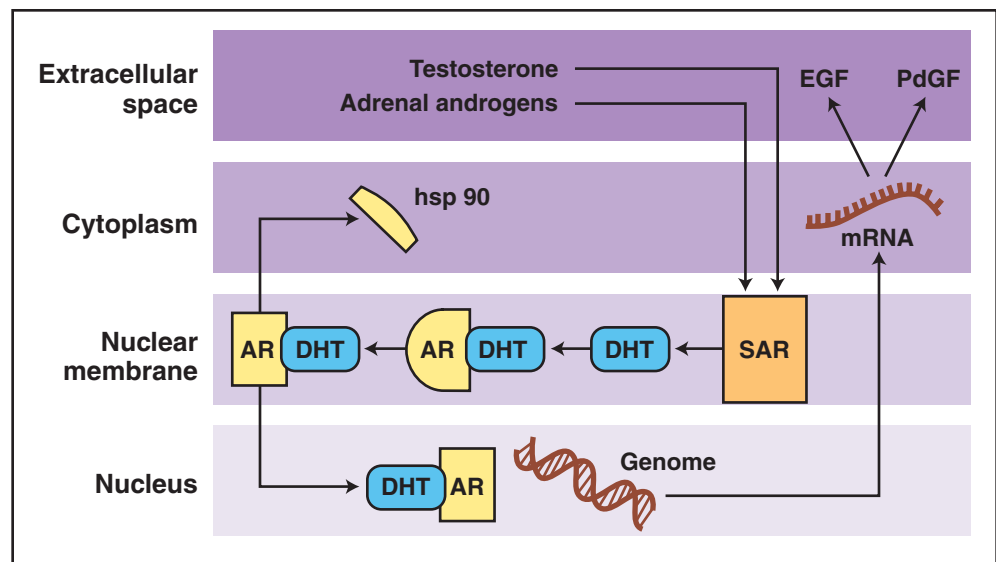


Figure 3: Testosterone enters the prostate and is converted to dihydrotestosterone (DHT). Dihydrotestosterone is the primary mediator of prostate growth. Within the prostate, testosterone is converted to DHT by the action of the enzyme 5 α -reductase (5AR). DHT binds to the androgen receptor (AR) to form a DHT-AR complex, which causes a cascade of intracellular events that leads to the expression of genes and production of growth and signaling factors that regulate cell division and proliferation in the prostate. Reprinted with permission from Andriole et al.¹⁷

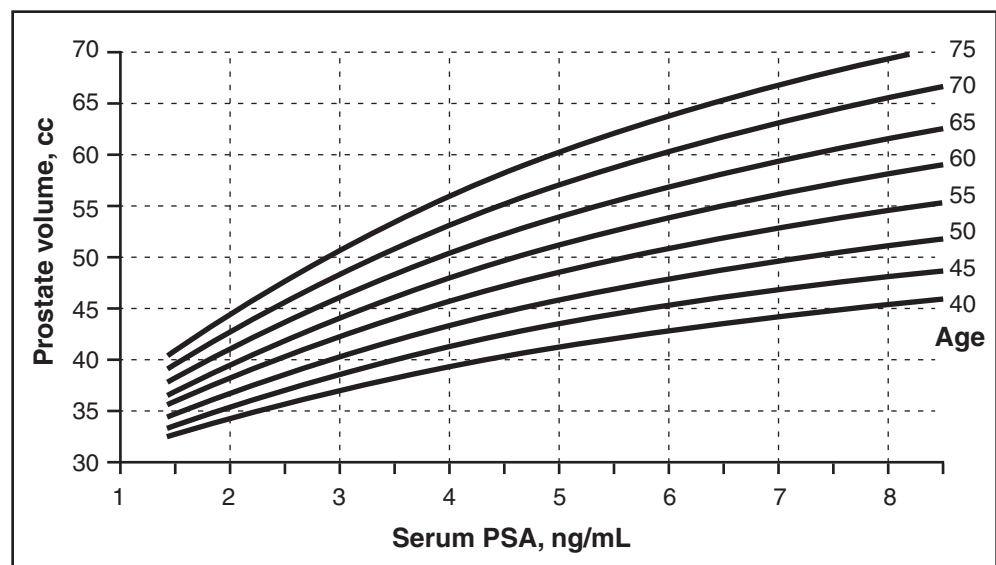


Figure 4: Age-stratified prostate volume predicts serum PSA levels. Relationship between prostate volume, serum PSA levels, and age in a model derived from baseline data of 4,627 men in finasteride trials. Age and prostate volume are the dominant influences on serum PSA levels once prostate cancer has been excluded. Reprinted with permission from Roehrborn et al.²⁹

PSA as a Surrogate for Prostate Volume

How can serum PSA level, which is widely considered a marker for prostate cancer, be a surrogate for prostate volume? A glycoprotein of high molecular weight (34 kD), PSA is produced exclusively by prostate epithelial cells.²⁷ Some PSA normally enters the systemic circulation via a transcapillary flux, and a low PSA level in male serum is considered to be normal. However, in certain

pathologic conditions, entry of PSA into the serum is increased. Prostate cancer, trauma, or inflammation may cause a PSA 'leak' into serum by disrupting the normal barriers. In benign prostatic hyperplasia, when the number of epithelial cells are increased, PSA also enters serum in increased quantities, perhaps because the driving force of the normal flux is increased under the sheer weight of the abnormal epithelial cell mass. While intergland variability in epithelial content is known,²⁸ large

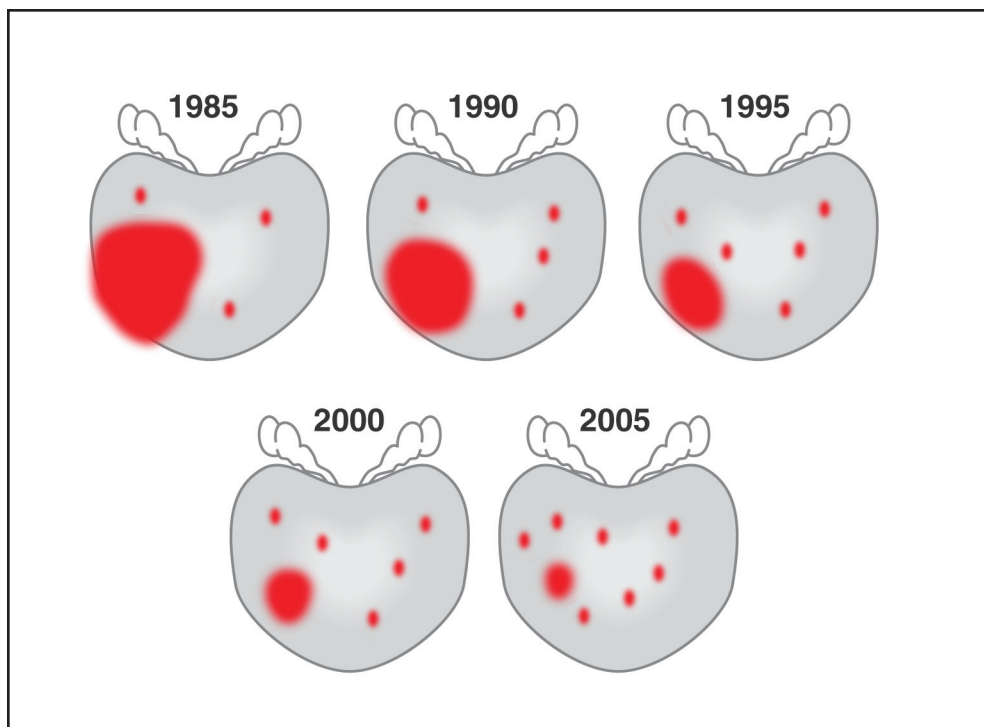


Figure 5: CaP then and now. Diagram showing effect of PSA testing, which began in the mid-1980s, on volume of index (largest) cancer in the prostate over ensuing years. The index cancer volume, shown as large red spot, has progressively decreased. In data from Stanford University, volume of the average index cancer found at radical prostatectomy has decreased from 5.3 cc to 2.4 cc over the past 20 years, mainly because of increasingly early diagnosis.³⁰

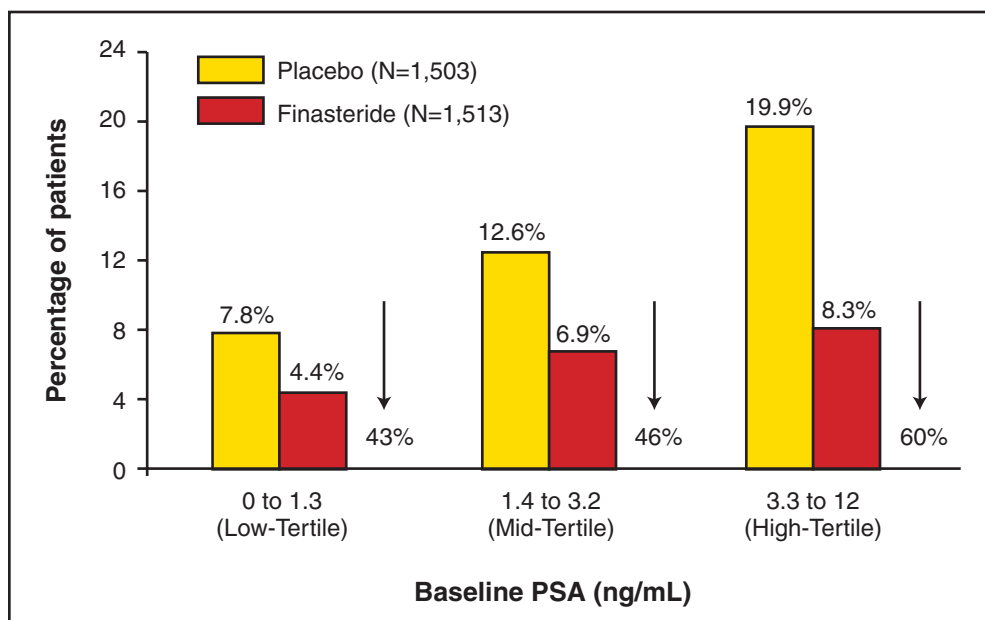


Figure 6: Risk of BPH-related surgery by PSA level in long-term finasteride trials.

Four-year incidence of BPH-related surgery in patients treated with placebo or finasteride, stratified in tertiles by baseline serum PSA. Arrows denote reduction in risk by the log rank test. Reprinted with permission from Roehrborn et al.³⁷

prostates generally contain more epithelial cells than small prostates and are associated with relatively high levels of PSA in serum.²⁹ The age-dependent relationship between serum PSA level and prostate volume in men with BPH is shown in Figure 4.

Over the past 20 years, PSA levels have increased in value as an index of BPH volume, as prostate cancer has begun to be detected earlier in its natural history, ie, in a low-volume state. In the words of one PSA pioneer, "Although the PSA era is probably over for

prostate cancer in the United States, it will remain an enduring marker for the amount of BPH and its rate of progression."³⁰

The effect of early detection of prostate cancer on the volume of cancers found over the past 20 years is shown in Figure 5. Cancer volume has decreased because of early detection, largely through PSA-driven biopsies. Today, serum PSA deriving from BPH overwhelms the serum PSA emanating from small cancers, reducing the value of PSA as a cancer screening test. Thus, the PSA-BPH/volume relationship holds true now more than ever, making the discovery of cancer-specific markers an urgent priority.

A relationship between benign prostate volume and serum PSA levels was established early by Stamey et al,³¹ when these investigators showed that for each gram of BPH tissue removed during prostatectomy, serum PSA level declines by approximately 0.3 ng/mL. Benson et al^{32,33} showed that serum PSA levels were consistently related to BPH volume (PSA density), and that when serum levels were inappropriately high relative to prostate volume, cancer was likely. According to Marks et al,³⁴ following a prostatectomy for BPH, serum PSA levels not only decreased to very low levels (new baseline of 0.4 to 0.7 ng/mL), but that these levels were unchanged for at least the next 5 years of follow-up, confirming the primacy of the BPH contribution to serum PSA levels. Magklara et al³⁵ demonstrated that gram-for-gram, benign prostate epithelium makes much more PSA than adjacent cancerous epithelium. In a study of thousands of men in BPH trials, Roehrborn et al²⁹ placed the association on a firm mathematic basis, demonstrating that serum PSA and prostate volume exhibit an age-dependent log-linear relationship. In that study, the receiver operating characteristics of a serum PSA level >1.5 ng/mL in predicting a prostate volume >30 cc to 40 cc (currently accepted criterion of EP) were excellent (area under curve=0.76).²⁹ Thus, if cancer is excluded, identification of men with an EP is possible using a serum PSA test.

Clinical Relevance of EP

Why is it important to identify men with an EP? First, men with EP are the ones most likely to experience accelerated growth of the gland.³⁶ Among the placebo-treated men in a large BPH trial, those with the highest PSA levels (and largest prostate volumes) experienced a 22% increase in volume over 4

years, while those with the lowest PSA levels (and smallest prostate volumes) experienced only a 7% growth rate.³⁶ Similar prostate growth was seen in men with elevated PSA levels, regardless of symptom status, in men enrolled in the Baltimore Longitudinal Study of Aging³⁸ and the Olmsted County Study.³⁹ Second, men with EP are those at greatest risk for BPH disease, as demonstrated in the MTOPS trial,⁴⁰ the finasteride long-term studies,⁴ and the Olmsted County Study.¹⁰ Of all the possible predictors of AUR, serum PSA level, the BPH volume surrogate, appears to be the most important.²⁷ In Figure 6, the value of serum PSA level as a predictor of BPH disease (and the influence 5ARI treatment can add) is shown in men from the long-term finasteride trials. And third, men with EP are those who respond best to treatment with a 5ARI.^{41,42} Although little information is available on 5ARI use in men with low prostate volumes, a recent report on dutasteride suggests that as long as prostate volume is >30 cc (corresponding to a serum PSA of approximately 1.5 ng/mL), drug effectiveness is maintained.⁴³

Pillars of BPH Prevention

In previous reports, the BPH prevention concept was centered around a logic, which has four supporting pillars (Figure 7).^{1,2} Having established from the first three pillars that histologic BPH may become a progressive and life-altering disease in certain, identifiable men, the remaining issue is demonstration that early use of medication can prevent BPH disease in the men at risk. Stated otherwise, what is the evidence that the tissue effects translate into a clinically meaningful benefit when the drugs are used in appropriate candidates for BPH disease prevention? To justify preventive use, measurable end points of BPH disease progression (AUR or need for surgery) should be detailed in long-term clinical trials where a 5ARI drug was compared with placebo in men who are minimally symptomatic at baseline. To date, the only relevant trial that has been completed is the Prostate Cancer Prevention Trial (PCPT),⁴⁴ in which almost 19,000 men were randomized to placebo or finasteride. In that trial, symptoms were irrelevant, except that severe prostatism was exclusionary; 86% of the men completed 7 years of follow-up. The primary end point of the study, a 25% reduction in period prevalence of CaP, was achieved, but prevention of BPH disease has not yet been reported

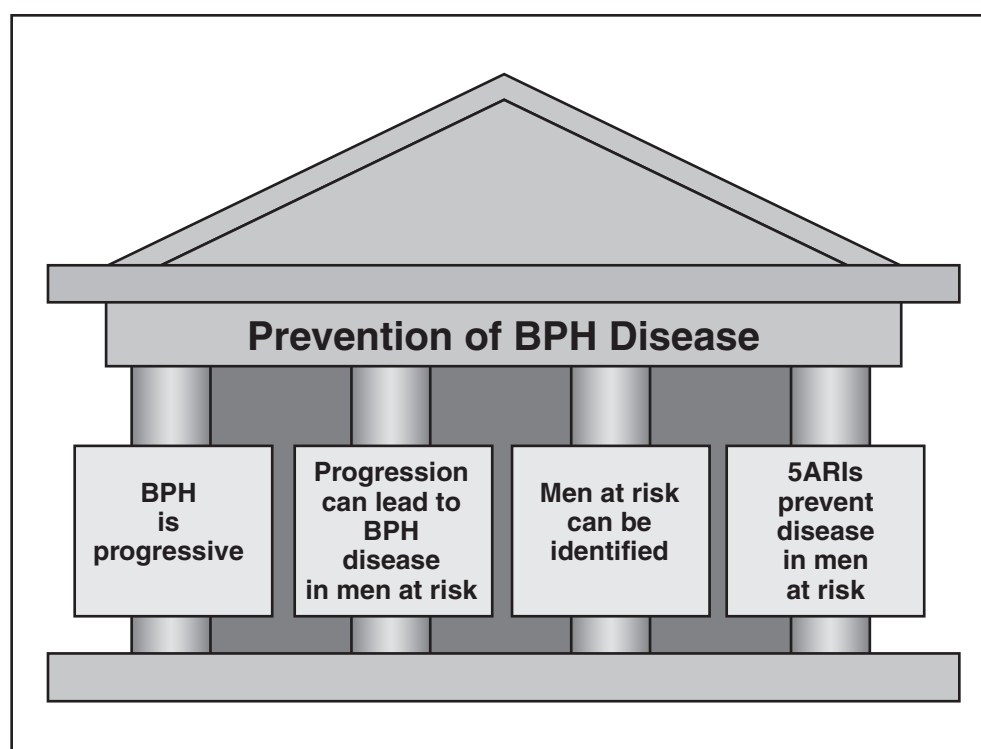


Figure 7: Pillars of BPH disease prevention. Modified from Marks.¹

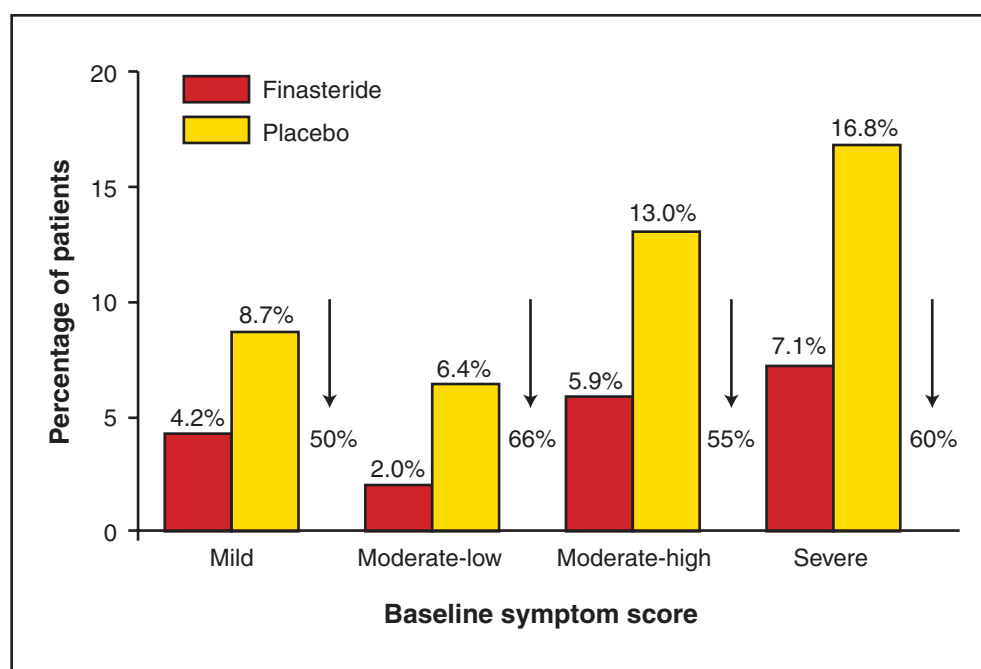


Figure 8: Incidence of BPH-related surgery by symptom score in long-term finasteride trials. Four-year incidence of BPH-related surgery in patients with baseline PSA levels of ≥ 1.4 ng/mL treated with either 5 mg of finasteride or placebo. Results are stratified by baseline quasi-AUA symptom score. Downward arrow indicates reduction in risk with finasteride. Reprinted with permission from Kaplan et al.⁴²

from this trial. Moreover, men with serum PSA levels >3.0 ng/mL (ie, men most likely to develop BPH disease) were excluded from participation in PCPT. Therefore, the BPH prevention concept may not be completely clarified from the PCPT data. Another cancer prevention study, the 4-year REDUCE trial (dutasteride vs placebo)⁴⁵ also enrolled men

with few BPH symptoms and with serum PSA levels up to 10 ng/mL, but this study has not yet been completed. A recent analysis from the Olmsted County Study showed that aspirin may also offer a degree of protection from BPH disease.⁴⁶ However, no clinical trial data are currently available for testing the BPH prevention hypothesis.

Current Evidence for Early Use of 5ARI Drugs

Despite the lack of a focused prevention study in men with few symptoms, certain data gleaned from BPH trials allow a partial evaluation of the concept that early use of a 5ARI can prevent BPH disease. For example, in the 4-year PLESS study,⁴² finasteride therapy prevented the need for BPH surgery in men with few symptoms to almost the same extent as in men with moderate or severe symptoms. In all symptom subgroups in that study, including men with only mild symptoms, finasteride treatment reduced the rate of surgery by 50% or more, compared with placebo (Figure 8). In the MTOPS study,⁴⁰ risk of BPH progression among men treated with finasteride was not related to symptom severity at baseline, ie, men with mild symptoms were protected to about the same extent as men with more advanced symptoms. Further, in a recent analysis of the placebo-treated men in the MTOPS study,⁴⁷ baseline symptoms were not a predictor of BPH disease progression, ie, men with mild symptoms were as likely to progress as men with more advanced symptoms.

An elevated serum PSA level not only correlates with a voluminous prostate,²⁹ but also appears to foretell future prostate growth³⁶ and increasing incidence of complications.³⁷ When serum PSA is <1.5 ng/mL, the chances of BPH disease are small, with increasing chances of disease as PSA increases from this level. Symptoms will cause men to seek medical attention, but symptoms are not the major determinant of long-term outcomes. In fact, serum PSA level (reflecting prostate volume) is clearly a more important predictor of BPH disease than any other factor or combination of factors.²⁷ Thus, in the absence of a trial designed specifically to test the value of 5ARI drugs in BPH disease prevention, the above stand as weighty evidence in favor of preventive treatment in all men whose serum PSA level is >1.5 ng/mL, regardless of symptom status.

Potential Disadvantages of 5ARI Drugs

The potential disadvantages of using 5ARI drugs to prevent BPH disease progression are fourfold. First, there are potential sexual side effects, which are uncommon, reversible, and do not occur with any frequency greater than with placebo after the first 6 months of treatment.⁴⁸ Second,

the drugs are not universally effective in preventing BPH progression, but they are clearly more than 50% effective in preventing AUR and the need for surgery in at-risk individuals.^{19,21} Third is the cost of the medication. A fourth concern is the possibility raised in the PCPT that 5ARI use contributes to the development of high-grade prostate cancers.⁴⁴ However, in the most recent analysis of PCPT data, Thompson et al⁴⁹ found that (1) finasteride heightens the sensitivity of PSA testing for cancer detection and (2) high-grade cancers are generally more common in men with high PSA levels (not completely suppressed by finasteride) and more likely to undergo biopsy than the other men. Thus, the increased incidence of high-grade cancer in the finasteride group is apparently a result of 'detection bias,' rather than any carcinogenic effect of the drug. Concern about a finasteride-induced grade-shift appears to be receding at the time of this writing.

Conclusion

The public health consequences and cost-benefit advantages of a 5ARI prevention strategy in BPH disease are presently difficult to quantify, but many individuals at risk, when given an option of a preventive, would likely elect treatment. The at-risk population includes primarily those men with serum PSA levels >1.5 ng/mL. Approximately one third of men more than 50 years old appear to have serum PSA levels in that range, according to the large national PSA database from Prostate Cancer Awareness Week.² At such a PSA level, an individual's risk of histologic BPH progressing to BPH disease may well exceed 20% to 30% over the next decade of life, judged by information derived from natural history studies.^{10,14,38} Overall benefits of early treatment would extend beyond AUR and surgery protection, and also would likely protect against the other aspects of BPH disease. This reasoning does not consider a reduction in prostate cancer risk from early use of 5ARI drugs, which would be another motivating factor for many. While not yet proven in focused clinical trials, prevention of BPH disease via early use of 5ARI drugs is a compelling concept. Many men, after making a personal risk-benefit assessment, will likely determine that a milligram of 21st century prevention is better than a pound of 'astonishing cure' from the last century.

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Self Test

This self-assessment test is presented as an educational adjunct to the monograph. Completion of this brief test will help reinforce the material you have read. Answers are elsewhere on this page.

1. BPH disease is characterized by:
 - a. acute urinary retention
 - b. intractable voiding symptoms
 - c. urinary bleeding
 - d. any of the above
2. Acute urinary retention and/or BPH-related surgery are:
 - a. eventually seen in most men
 - b. relatively common occurrences
 - c. not seen before the age of 75 years
 - d. related to sexual activity
3. The primary mediator of prostate growth is:
 - a. testosterone
 - b. epinephrine
 - c. dihydrotestosterone
 - d. cortisol
4. Drugs that shrink the prostate are known as:
 - a. antihistamines
 - b. α -blockers
 - c. nonsteroidal anti-inflammatory agents
 - d. 5α -reductase inhibitors
5. Prostate volume:
 - a. increases with age
 - b. is indicated by serum PSA level
 - c. correlates with development of BPH disease
 - d. all of the above

Self-Test Answers for This Issue:

1. d 2. b 3. c 4. d 5. d

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