Measurement of prostate-specific antigen

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INTRODUCTION

Prostate-specific antigen (PSA) is a glycoprotein that is expressed by both normal and neoplastic prostate tissue. PSA is consistently expressed in nearly all prostate cancers, although its level of expression on a per cell basis, especially in very poorly differentiated prostate cancers, is lower than in normal prostate epithelium. The absolute value of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment; its use as a screening method to detect prostate cancer is also common, although controversial. (See "Clinical presentation and diagnosis of prostate cancer" and "Screening for prostate cancer".)

The measurement of PSA, causes of abnormal values, and advances in PSA testing will be reviewed here. Recommendations for the clinical use of PSA testing in screening for prostate cancer are presented separately. (See "Screening for prostate cancer".)

PSA EXPRESSION AND PROCESSING

Under normal conditions, PSA is produced as a proenzyme (proPSA) by the secretory cells that line the prostate glands (acini) and secreted into the lumen, where the propeptide is removed to generate active PSA. The active PSA can then undergo proteolysis to generate inactive PSA, of which a small portion then enters the bloodstream and circulates in an unbound state (free PSA). Alternatively, active PSA can diffuse directly into the circulation where it is rapidly bound by protease inhibitors, including alpha-1-antichymotrypsin (ACT) and alpha-2-macroglobulin [1,2].

Although generating less PSA per cell than normal tissue, prostate cancer lacks basal cells, resulting in the disruption of the basement membrane and normal lumen architecture. As a result, the secreted proPSA and several truncated forms have direct access to the circulation, resulting in more PSA "leaked" into the blood and a larger fraction of the PSA produced by malignant tissue escapes proteolytic processing (ie, activation of proPSA to active PSA and degradation of active PSA to inactive PSA).

In men with a normal prostate (ie, no cancer and no major inflammation/infection), the majority of free PSA in the serum reflects the mature protein that has been inactivated by internal proteolytic cleavage. By contrast, this cleaved fraction is relatively decreased in prostate cancer. Thus, the percentage of free or unbound PSA is lower in the serum of men with prostate cancer (and, conversely, the amount of complexed PSA is higher) compared with those who have a normal prostate or benign prostatic hyperplasia (BPH) [3-6]. This finding has been exploited in the use of the ratio of free to total PSA and complexed PSA (cPSA) as a means of distinguishing between prostate cancer and BPH as a cause of an elevated PSA. (See 'Serum free and bound PSA' below and 'Complexed PSA' below.)

PSA MEASUREMENT

A number of assays are available to measure serum PSA; although the exact value that is considered "abnormal" is highly controversial, historically a concentration above 4 ng/mL was considered abnormal in most. (We describe PSA

values in ng/mL throughout this topic, but this is equivalent to the SI units of mcg/L; that is, 4 ng/mL = 4 mcg/L.) Although concerns have been raised regarding calibration of the various assays, this is of little clinical relevance, except that it makes it more difficult to interpret subtle changes in PSA over time (ie, PSA velocity) when those changes involve PSA values that were measured using different assays [7,8].

Age-specific reference ranges — In men without prostate cancer, serum PSA reflects the amount of glandular epithelium, which in turn reflects prostate size. Thus, as prostate size increases with increasing age, the PSA concentration also rises; it increases at a faster rate in older adult men [9]. In one study of 471 men, the serum PSA concentration increased by approximately 3.2 percent (0.04 ng/mL) per year for a healthy 60-year-old [10]. As a result, different normal reference ranges may be appropriate based upon a man's age [11,12]:

- 40 to 49 years – 0 to 2.5 ng/mL
- 50 to 59 years – 0 to 3.5 ng/mL
- 60 to 69 years – 0 to 4.5 ng/mL
- 70 to 79 years – 0 to 6.5 ng/mL

These age-specific reference ranges have been proposed as a means of improving specificity and positive predictive value of the serum PSA in screening for prostate cancer.

The best cutoff to separate cancer from benign causes of elevated PSA remains hotly debated. The use of a higher upper range of normal for older men reduces the sensitivity of serum PSA testing for the detection of early prostate cancer, while increasing specificity. Whether these higher cutoffs should be used, which could result in missing clinically significant cancers in older men, remains controversial. Additionally, although there is evidence suggesting PSA-based screening may be beneficial for some, this remains a controversial area. (See "Screening for prostate cancer".)

Men from different ethnic and racial groups who do not have cancer have different average PSA concentrations. In particular, Black men without prostate cancer tend to have higher PSA values than White men without prostate cancer. It has been proposed that the definition of a "normal" PSA should vary by race using race-specific reference ranges [13]. However, different reference ranges by race were never widely adopted and they are not commonly used in clinical practice.

Other effects on normal range — Weight appears to be associated with PSA concentration. In population-based studies of men without prostate cancer, increasing body mass index (BMI) is associated with a lower mean PSA concentration [14-17].

One study looked at PSA concentration, total mass of PSA in the blood (ie, the amount of PSA calculated as PSA concentration multiplied by plasma volume), and plasma volume in three separate cohorts totaling nearly 14,000 men, all with early stage prostate cancer treated by radical prostatectomy [18]. The study found that although men with higher BMI had lower PSA concentrations, they had a similar amount of circulating PSA mass as men with lower BMI [18]. Thus, the lower PSA concentrations in men with higher BMI (up to 20 percent lower in very obese men) may have been due to increased plasma volume in men with higher BMI leading to hemodilution of the PSA.

The implications of this observation for screening men with a high BMI are uncertain, but it is possible that the normal PSA range should be lower in men with a high BMI. Additionally, there appears to be an association between increasing obesity and increasing prostate cancer aggressiveness. (See "Risk factors for prostate cancer", section on 'Obesity'.)

Medications — Several classes of medication may affect serum PSA levels:

- 5-alpha-reductase Inhibitors – Finasteride and dutasteride, inhibitors of 5-alpha-reductase, produce an approximately 50 percent or greater decrease in serum PSA during the first three to six months of therapy, which persists as long as the drug is continued. This is probably due to direct interference by these drugs with the prostatic intracellular androgen response mechanism [19], although these agents actually reduce prostate

size which likely contributes to the lower PSA levels as well. Thus, the appropriate serum PSA reference range for men receiving finasteride or dutasteride needs to be adjusted [20]. Even the doses used to treat male-pattern baldness (eg, 1 mg daily of finasteride versus 5 mg daily for benign prostatic hyperplasia [BPH]) result in similar declines in PSA such that the PSA reference range will also need to be adjusted [21].

Longitudinal results from the Prostate Cancer Prevention Trial suggest that PSA values should be corrected by a factor of 2 for the first two years of finasteride therapy and by 2.5 for longer-term use [22]. However, it is important to note that a median drop in PSA of 50 percent means that half the men have PSA values that fall by less than 50 percent, and thus simply doubling the PSA (by multiplying the on-finasteride PSA result by two) would result in an apparent increase in PSA values for half the men. There is increasing interest in examining change in PSA in men on finasteride or dutasteride. An analysis from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial found that after establishing a new baseline six months after starting dutasteride, any rise from that point forward, especially rises >0.5 ng/ml, was associated with a higher risk of prostate cancer or high-grade prostate cancer compared with men in whom the PSA did not rise from the new baseline [23,24].

These results suggest that any rising PSA on dutasteride, especially rises >0.5 ng/ml and even if in the normal range, should prompt further evaluation. Whether these data apply equally to finasteride is unclear, and it is also uncertain whether the correction factor for finasteride applies to dutasteride. However, given the similar mechanisms of action, it seems prudent to evaluate PSA similarly in patients on either medication. (See "Medical treatment of benign prostatic hyperplasia".)

- NSAIDs and acetaminophen – In a population-based study of 1319 men, those who were regularly taking nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen had lower PSA levels (0.10 ng/mL and 0.28 ng/mL respectively, compared with men taking neither drug) [25]. There were few men regularly taking acetaminophen, and only the results for NSAIDs were statistically significant. The link between lower PSA and NSAIDs was further validated in a separate study of 1864 men [26]. This latter study also found that longer duration of NSAID use was associated with even lower PSA values. The degree to which this may alter PSA screening remains to be determined. The mechanism through which this might occur is not known, although it could relate to the antiinflammatory properties of these agents.

- Statins – A study in 1214 men found that median PSA levels dropped by 4.1 percent over approximately one year after starting a statin medication, compared with the natural history of PSA to rise by 3.2 percent per year [27]. The decline in PSA was correlated with the decline in low-density lipoprotein (LDL) cholesterol, with greater LDL cholesterol declines being associated with greater PSA declines. This drop in PSA was also correlated with the dose of statin given and the baseline starting PSA. As an example, men with a baseline PSA >2.5 ng/mL who were in the quartile with the greatest decrease in LDL cholesterol (>41 percent) experienced a median 17.4 percent decline in PSA. These results have subsequently been validated in several studies [26,28].

- Thiazides – A cross-sectional study of 1864 men found that thiazide diuretic use was associated with lower PSA levels [26]. Longer-term use was associated with even lower PSA levels, with five years of use being associated with a 26 percent reduction in serum PSA levels. These results are preliminary.

Whether the relatively small changes in PSA with NSAIDs, acetaminophen, statins, and thiazides have clinical relevance is unknown. It is uncertain whether the reduction in PSA reflects an actual reduction in prostate cancer risk or rather an effect on PSA production that would alter the screening characteristics of PSA measurement. At the least, interim initiation of any of these medications may affect serial PSA measurement and so should be taken into account when evaluating PSA changes over time.

Random variation — PSA levels that are measured repeatedly over time may vary both because of imprecision in the analysis and biologic variability where the true PSA level in a given man is different on different measurements. This could potentially lead to an apparent rise in PSA level when no actual rise had occurred.

A study of prior PSA results in 3568 men with a PSA concentration below 2.0 ng/mL during a fourth round of PSA screening estimated that the average analytic variation in PSA was approximately 6 percent and the average biologic variation was less than 14 percent [29]. A change in PSA of more than 30 percent in men with a PSA initially below 2.0 ng/mL was likely to indicate a true change beyond normal random variation.

CAUSES OF AN ELEVATED SERUM PSA

The major causes of an elevated serum PSA include:

- Benign prostatic hyperplasia (BPH)
- Prostate cancer
- Prostatic inflammation/infection
- Perineal trauma

Benign prostatic hyperplasia — The most common explanation for an elevated serum PSA is BPH because of the very high prevalence of this condition in men over the age of 50 (figure 1). BPH produces more PSA per gram than normal prostate tissue. (See "Epidemiology and pathophysiology of benign prostatic hyperplasia".)

One illustrative study compared 148 men with a serum PSA above 4.0 ng/mL, findings suspicious for cancer on digital rectal examination (DRE), and multiple negative biopsies, with 64 men who had a suspicious DRE, multiple negative biopsies, and a serum PSA of 4.0 ng/mL or less [30]. The higher PSA group had larger prostates (68 versus 33 mL), and a simultaneous regression analysis determined that prostate size accounted for 23 percent of the variance in serum PSA concentration.

Serum PSA levels overlap considerably in men with BPH and those with prostate cancer. As an example, one report retrospectively examined preoperative serum PSA in 187 men with a histologic diagnosis of BPH on a transurethral resection of the prostate (TURP) specimen and 198 men with organ-confined prostate cancer as determined by step-section analysis of a radical prostatectomy specimen [31]. The median serum PSA concentrations were 3.9 (range 0.2 to 55) and 5.9 ng/mL (range 0.4 to 58), respectively. Although this difference was statistically significant, the distribution of serum PSA values in both groups overlapped considerably with a clustering of PSA values below 10.0 ng/mL (90 and 73 percent, respectively).

A potentially confounding problem is that medical treatment for BPH can reduce serum PSA concentrations. (See 'Medications' above.)

Prostate cancer — Studies in the 1980s confirmed that serum total PSA could be used to identify men with prostate cancer. As a screening tool, serum PSA was clearly more sensitive than the DRE, but it lacked specificity. Furthermore, although the majority of prostate cancers express PSA, between 20 and 50 percent of men with newly diagnosed screen-detected prostate cancers in the United States have serum PSA values below 4.0 ng/mL [32-35]. Those cancers that are detected at a time when the serum PSA is less than 4.0 ng/mL are more likely to be organ-confined than cancers detected at a time when the PSA level is >4.0 ng/mL, and they have a better prognosis [35,36]. A complete review of PSA testing for prostate cancer screening is discussed separately. (See "Screening for prostate cancer".)

Prostatic inflammation and infection — Prostatitis with or without active infection is an important cause of an elevated PSA [30,37-40]; levels as high as 75 ng/mL have been reported [41]. Thus, many clinicians will initially treat a man with an isolated elevated serum PSA with antibiotics for a presumed diagnosis of prostatitis and then obtain a repeat serum PSA. One study tested this approach by randomly assigning 216 men with either a positive (n = 108) or negative (n = 108) expressed prostate secretion culture to antibiotics, antiinflammatory drugs, or a control group [42]. Only in the group of men with a positive culture assigned to antibiotics did the PSA decrease. Thus, for men with a negative culture, antibiotics had no effect on PSA. Likewise, antiinflammatory drugs had no effect on PSA regardless of the culture results. Another randomized trial in asymptomatic men with an elevated PSA also found no

clear evidence of benefit in treating with six weeks of fluoroquinolone antibiotics [43]. These findings support the observation that a reduction in PSA levels can be expected if prostatitis with infection was solely responsible; however, prostatitis can often exist without active infection, in which case the PSA will not uniformly normalize. Based upon these and other studies showing no benefit to using antibiotics for asymptomatic men with an elevated PSA, the American Urological Association, as part of their Choosing Wisely campaign, has expressly stated, "Don't treat an elevated PSA with antibiotics for patients not experiencing other symptoms." (See "Acute bacterial prostatitis".)

In one of the studies cited above, evaluating men with suspicious findings on DRE but with multiple negative prostate biopsies, both acute and chronic inflammation were more prevalent in those with a serum PSA >4.0 ng/mL compared with those with lower values (63 versus 27 percent and 99 versus 77 percent, respectively) [30]. The percentage of free PSA may be less affected by the presence of inflammation, particularly when the total serum PSA is less than 10 ng/mL [44]. However, at least one study suggests that the free to total ratio of serum PSA is unable to distinguish chronic inflammation from prostate cancer, as both conditions lower the percentage of free PSA as would be expected in that inflammation leads to elevated serum PSA in a similar fashion as prostate cancer: through disruption of the basal membrane and increased leakage of "immature" PSA into the blood stream [45]. (See 'Serum free and bound PSA' below.)

Perineal trauma and sexual activity — Any perineal trauma can increase the serum PSA. DRE may cause minor transient elevations that are clinically insignificant. As an example, one study of 2750 healthy men over the age of 40 undergoing DRE divided patients into four groups based upon their initial serum PSA [46]. The two groups with the lowest initial serum PSA values (0.1 to 4 and 4.1 to 10 ng/mL) had statistically insignificant changes in the serum PSA after DRE, while PSA increases in the group with an initial serum PSA 10.1 to 20 ng/mL showed a trend toward statistical significance, and those with an initial serum PSA greater than 20 ng/mL had statistically significant increases after DRE. The PSA increase in the two groups with the highest serum values was not clinically relevant, since they did not change ultimate management. Thus, it is reasonable to perform PSA testing without regard to whether a patient has had a recent DRE.

A study of PSA measurements 30 minutes after one minute of prostatic massage found that massage increased total PSA and free PSA levels to a greater extent than complexed PSA levels [47]. Thus, it is advisable to check PSA levels prior to performing a prostate massage.

Mechanical manipulation of the prostate by cystoscopy, prostate biopsy, or TURP can more significantly affect the serum PSA. This was illustrated in a study of 101 men who underwent one of these procedures [48]. The median time required for the serum PSA to return to baseline after prostate biopsy was 15 days (range 5 to 21 days) and 17 days (range 3 to 30+ days) for men with and without prostate cancer, respectively, and 18 days (range 12 to 30+ days) for men who underwent TURP. The median change in serum PSA was of a lesser magnitude following flexible or rigid cystoscopy. Thus, a serum PSA determination after either a flexible or rigid cystoscopy is reliable, but a serum PSA determination should not be obtained for at least six weeks after either a prostate biopsy or TURP.

Vigorous bicycle riding has been reported to cause substantial elevations in the serum PSA [49], but this is not a consistent finding [50,51]. A 2015 meta-analysis including eight studies and 912 men found that bicycling had no significant effect on PSA levels [52].

Sexual activity can minimally elevate the PSA (usually in the 0.4 to 0.5 ng/mL range) for approximately 48 to 72 hours after ejaculation [53]. We do not usually ask men to abstain from sexual activity prior to PSA measurement. However, if an initial measurement is high enough to potentially prompt an intervention (ie, biopsy), but close to a borderline value, it is not unreasonable to repeat the PSA measurement after having the man abstain from ejaculation for at least 48 hours. (See "Screening for prostate cancer".)

Other — Although PSA has traditionally been thought to be prostate gland-specific, some studies have documented the presence of PSA in the serum and tumors of women with breast cancer [54,55] and rarely other tumors, most

notably salivary gland tumors [56]. The significance of this finding is unclear.

ADVANCES IN PSA TESTING

Emerging concepts regarding PSA testing that may help refine the interpretation of an elevated concentration include:

- PSA density
- PSA velocity
- Free versus complexed or bound PSA

These modifications would presumably be most useful for prostate cancer screening when the total PSA is 2.5 to 10.0 ng/mL, the range in which decisions regarding further diagnostic testing are most difficult. However, in clinical practice, the use of these techniques is not consistent and remains debated. (See "Screening for prostate cancer".)

PSA density — To more directly compensate for BPH and prostate size, transrectal ultrasound (TRUS) has been used to measure prostate volume. Serum PSA is then divided by prostate volume to give a PSA density, with higher PSA density values (greater than 0.15 ng/mL/cc) being more suggestive of prostate cancer while lower values are more suggestive of benign prostatic hyperplasia (BPH) [57,58].

While an early study suggested that PSA density was a promising method for distinguishing patients with benign and malignant prostate disease [57,59], subsequent reports have found considerable overlap in PSA densities between these groups [60]. One multicenter study that compared PSA density with PSA for the early detection of prostate cancer found that almost one-half of the cancers would have been missed using 0.15 ng/mL/cc as a cutoff for biopsy [61].

Another report of 1809 men with untreated prostate disease found that the sensitivity of PSA density could improve with adjustment of the cutoff value for different ranges of total PSA: 0.1 ng/mL/cc for total PSA 4 to 10 ng/mL and 0.19 ng/mL/cc for total PSA 10 to 20 ng/mL [62]. In this cohort, 111 of 401 men (27.7 percent) with total PSA in the 2 to 4 ng/mL range had prostate cancer. PSA density measurement performed better than free PSA measurement (see 'Serum free and bound PSA' below) in identifying cancer in patients with total PSA in the 2 to 4 ng/mL range. This was not a screening study, and the applicability of PSA density determinations for asymptomatic men with screening total PSA in the 2 to 4 ng/mL range is questionable.

There are inherent difficulties in measuring PSA density, which include errors of prostatic volume measurement with TRUS and an intrapatient variation of up to 15 percent in PSA density with repeated measurements [63]. Furthermore, although PSA density can reliably differentiate between large groups of patients with BPH and prostate cancer, the ability to extrapolate these data to the individual patient is quite limited. Most importantly, the requirement for TRUS substantially increases cost and discomfort and is impractical for widespread screening purposes.

PSA velocity — Another approach has been to assess the rate of PSA change over time (the PSA velocity). An elevated serum PSA that continues to rise over time is more likely to reflect prostate cancer than one that is consistently stable [64]. In one study, a PSA velocity cutoff of 0.75 ng/mL per year distinguished patients with prostate cancer from those with either BPH or no prostate disease with a specificity of 90 and 100 percent, respectively [65]. A further study from the same group found that when PSA was <4 ng/mL, a PSA velocity >0.35 ng/mL per year measured over several years was associated with a high risk of death from prostate cancer 15 years later [66]. Similarly, another series of studies from a different group found that among men with prostate cancer, a PSA velocity >2 ng/mL per year in the year prior to diagnosis was associated with an increased risk of death from prostate cancer after radical prostatectomy or radiation therapy [67,68].

A community-based study examined PSA velocity in 1851 men with a normal DRE who underwent prostate biopsy for an elevated PSA [69]. In this study, very high PSA velocities (above 3.0 ng/mL per year) were associated with prostatic

inflammation as the etiology of the elevated PSA, and thus a reduced risk of prostate cancer on biopsy.

In practicality, the clinical usefulness of PSA velocity is in part limited by intrapatient variability in the serum PSA; at least three consecutive measurements should be performed [70]. A longer time over which values are measured can help reduce the general variation (ie, "noise") in the PSA measurements. Depending upon the magnitude of the abnormal serum PSA, it is likely that a patient with an initially abnormal level would undergo prostate biopsy before waiting for a second measurement to be performed one year later. Said in a different way, a rapid PSA velocity will quickly result in an abnormal PSA level, which would be further evaluated due to the PSA elevation alone even in the absence of a rapid velocity. Furthermore, men with cancer often have a PSA velocity of less than 0.75 ng/mL per year, especially those with lower PSA levels [71,72]. Multivariate and receiver operator characteristic (ROC) analyses as well as a systematic review suggest that calculation of PSA velocity and PSA doubling time are of limited value in screening [73-76], though some studies do suggest they may be useful in detecting the most aggressive cancers [66].

Serum free and bound PSA — As noted previously, prostate cancer is associated with a lower percentage of free PSA in the serum as compared with benign conditions. (See 'PSA expression and processing' above.)

The percentage of free PSA (free/total PSA ratio [f/t PSA]) has been used to improve the sensitivity of cancer detection when total PSA is in the normal range (<4 ng/mL) and to increase the specificity of cancer detection when total PSA in the "gray zone" (4.1 to 10 ng/mL). In this latter group, the lower the value of f/t PSA, the greater the likelihood that an elevated PSA represents cancer and not BPH. As an example, in one study of men with PSA values in this range, the probability of cancer in men with a f/t PSA below 10 percent was 56 percent, compared with only 8 percent of men with a value >25 percent [77].

As with PSA, there is no absolute f/t PSA cutoff that completely discriminates prostate cancer from BPH. The optimal cutoff value for f/t PSA is unclear and depends upon whether optimal sensitivity or specificity is sought [78,79]. The higher the cutoff value, the greater the sensitivity (ie, fewer cancers missed), but the lower the specificity (greater number of false positives).

Free PSA may be useful for risk stratification in men with prostate cancer. A lower percentage of f/t PSA may be associated with a more aggressive form of prostate cancer. This was illustrated in a study that examined banked frozen serum from 20 men with prostate cancer [80]. Ten years before the diagnosis of cancer, at a time when the total PSA was not different between those who ultimately developed aggressive versus nonaggressive tumors (aggressive defined by clinical stage T3 disease, nodal or bone metastases, pathologically positive margins, or Gleason score of 7 or greater), there was a statistically significant difference in the percentage of f/t PSA between the two groups. All eight men with aggressive cancers had a f/t PSA of ≤14 percent, compared with only two of six (33 percent) with nonaggressive cancer.

Complexed PSA — Assays have been developed for alpha1-antichymotrypsin (ACT)-complexed PSA (cPSA) [81-83]. Such an assay would theoretically provide a similar enhanced degree of specificity as the f/t PSA but require only the measurement of a single analyte. In addition to the obvious economic advantage, the variability associated with nonuniformity of different manufacturers' assays for total or f/t PSA could be avoided.

Most [84-90], but not all [91-94], reports suggest that cPSA outperforms both total PSA and the f/t PSA, with similar sensitivity but a higher specificity. In one representative series, the diagnostic utility of the Bayer Immuno-One cPSA assay was compared with the Tandem R free and total PSA assay by using archival sera obtained from 300 men, 75 of whom had biopsy-confirmed prostate cancer [84]. When compared with total PSA (cutoff ≥4.0 ng/mL), cPSA (cutoff 3.75 ng/mL) provided significantly higher specificity (48 versus 33 percent) with only a modest decrease in sensitivity (81 versus 83 percent). Although a higher specificity could be achieved with a 25 percent cutoff for f/t PSA (44 percent), sensitivity was only 77 percent. Stated another way, if only cPSA were measured, one cancer would have been missed and 35 negative biopsies avoided; by contrast, using a f/t PSA cutoff of 25 percent, five cancers would have been missed and 25 biopsies avoided.

For men with total PSA in the diagnostic gray zone (4.0 and 10.0 ng/mL), the use of cPSA alone would have missed one of the 36 men with cancer who would be identified using total PSA, and 34 biopsies could be avoided. By contrast, f/t PSA alone would also have missed one cancer, but eliminated biopsy in only 20 men. The utility of cPSA in men with a lower total PSA (2 to 4 ng/mL) is under study; there are conflicting data as to whether cPSA improves specificity compared with f/t PSA [90,95].

Others have not been able to show improved specificity from the use of cPSA [91-94]. In at least one case, the discrepancy might be explained by selection bias and the inability to demonstrate higher total PSA levels in men with malignancy compared with benign disease [91].

Complexed PSA has been approved for the monitoring of men with prostatic carcinoma [96]. The utility of cPSA for screening is uncertain and is not routinely used in current practice.

Percent [-2]proPSA — As discussed above (see 'PSA expression and processing' above), PSA is initially produced as proPSA, and this form can preferentially leak into the blood stream in men with prostate cancer. One specific isoform of proPSA is [-2]proPSA, which is unbound and potentially higher in men with prostate cancer. Based upon this observation, there has been growing interest in using the ratio of [-2]proPSA to free PSA (expressed as percent [-2]proPSA or %[-2]proPSA) for prostate cancer screening. One multicenter study of 566 men undergoing biopsy found that %[-2]proPSA significantly outperformed both total PSA and percent free PSA [97]. At 80 percent sensitivity, %[-2]proPSA had 52 percent specificity, compared with 30 percent for PSA and 29 percent for percentage of free PSA. Percent [-2]proPSA is approved by the European Union for prostate cancer detection and is being evaluated in the United States by the Food and Drug Administration.

Prostate Health Index (PHI) — [-2]proPSA has been combined with free PSA to generate a new prostate cancer risk assessment called the Prostate Health Index or phi. In a multicenter study of 658 men undergoing prostate biopsy for a PSA between 4 and 10 ng/mL that compared the performance of PSA, free PSA, [-2]proPSA, and phi, phi was the best predictor of any prostate cancer, high-grade cancer, and clinically significant cancer [98]. However, in a multicenter study of 489 men undergoing radical prostatectomy, while phi and [-2]proPSA were significant predictors of adverse pathology, they provided no net clinical benefit in decision analysis models [99]. This suggests that while they may be statistically linked with aggressive disease, they may not meaningfully impact clinical decision making. As such, the role of phi in prostate cancer management remains to be fully determined.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Screening for prostate cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Benign prostatic hyperplasia (enlarged prostate) (The Basics)" and "Patient education: Prostate cancer screening (PSA tests) (The Basics)")
- Beyond the Basics topics (see "Patient education: Benign prostatic hyperplasia (BPH) (Beyond the Basics)" and "Patient education: Prostate cancer screening (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Serum prostate-specific antigen (PSA) is a valuable marker for prostate cancer. However, its sensitivity and specificity are not perfect as a screening tool. An elevated serum PSA value can also be due to many other causes. (See 'Causes of an elevated serum PSA' above.)
- Emerging concepts regarding PSA testing include the use of PSA density and PSA velocity, although these have not been widely adopted. (See 'Advances in PSA testing' above.)
- One promising method to improve specificity of PSA testing for men who have total PSA values 4 to 10 ng/mL and to improve sensitivity at levels below 4 ng/mL is to include PSA isoforms such as the free to total PSA ratio, the amount of complexed PSA, and the percent [-2]proPSA, with the last appearing to be the most promising. (See 'Serum free and bound PSA' above and 'Percent [-2]proPSA' above.)
- Recommendations for the clinical use of PSA testing in screening for prostate cancer are presented separately. (See "Screening for prostate cancer".)

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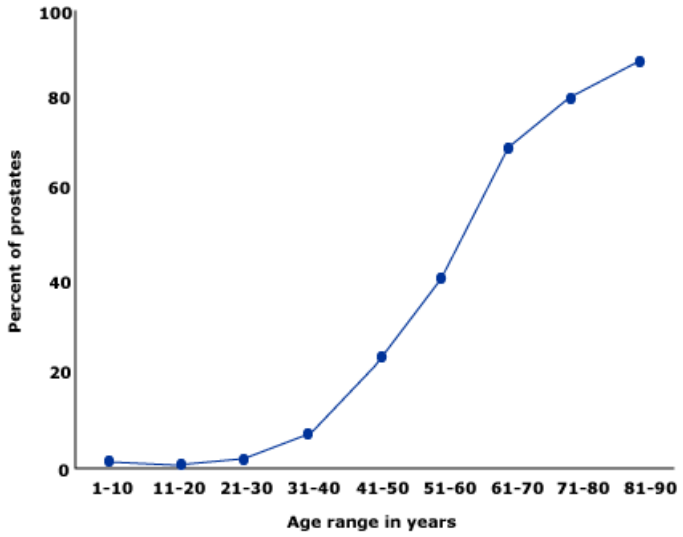
Topic 7568 Version 33.0

GRAPHICS

Prevalence of benign prostatic hyperplasia pathology with age



Age-associated increase in pathologic evidence of benign prostatic hyperplasia in 1075 men at autopsy. The percentage with benign prostatic hyperplasia was determined during 10-year intervals from 5 different studies; the mean values are shown.

Data from Berry, SJ, Coffey, DS, Walsh, PC, et al. The development of human benign prostatic hyperplasia with age. J Urol 1984;132:474.

Graphic 55614 Version 2.0

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