PROSTATE SPECIFIC ANTIGEN (PSA)

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- Prostate-specific antigen (PSA) is a protein produced by prostate cells.
- A glycoprotein produced primarily by the epithelial cells that line the acini and ducts of the prostate gland.
- PSA is a neutral serine protease.
- Liquefaction of the seminal fluid coagulum.
- Important role in fertility.
PSA is concentrated in prostatic tissue, and serum PSA levels are normally very low.
The highest amounts found in seminal fluid; some PSA escapes the prostate and can be found in the serum.
Disruption of the normal prostatic architecture, such as by prostatic disease, allows greater amounts of PSA to enter the general circulation.
This serum component has been used in the management of prostate diseases, especially Prostate Cancer.
- PSA levels have been used in screening of men for prostate cancer
- Studies underway to determine if PSA screening actually makes any real difference in the detection and survival
- Prior to the PSA era
  - 70% of men diagnosed with prostate cancer had extraprostatic or metastatic disease
  - Abnormality in the prostate had to be palpably evident before a biopsy was performed
Advent of PSA evaluation

- Fewer than 3% of men have metastases at the time of diagnosis
- 75% of men have nonpalpable cancer. In this latter group, the cancer was detected based on biopsy performed because of a rapidly rising or markedly elevated PSA level.
PSA testing

- Helps in the early diagnosis of Ca Prostate
- Assists in assessing the response to therapy
- Determining tumor progression
- Screening for prostate cancer → *most controversial role*
The standard PSA reference range is 0-4 ng/mL.

PSA levels tend to increase with age

- Increase is related to prostate volume
- Most PSA is made in the transition zone (TZ) of the prostate
- This region’s volume increases in men with BPH.

PSA is not a Tumour Marker
### Correlation between Serum PSA Levels and the Presence of Detectable Prostate Cancer in 45- to 80-Year-Old Men

<table>
<thead>
<tr>
<th>Serum PSA (ng/mL)</th>
<th>Total number of men</th>
<th>Number of men with PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>%</td>
</tr>
<tr>
<td>&gt;30</td>
<td>48</td>
<td>0.6</td>
</tr>
<tr>
<td>10.1 - 50.0</td>
<td>191</td>
<td>2.4</td>
</tr>
<tr>
<td>7.1 - 10.0</td>
<td>177</td>
<td>2.8</td>
</tr>
<tr>
<td>5.1 - 7.0</td>
<td>294</td>
<td>3.7</td>
</tr>
<tr>
<td>4.1 - 5.0</td>
<td>255</td>
<td>3.8</td>
</tr>
<tr>
<td>3.1 - 4.0</td>
<td>473</td>
<td>5.9</td>
</tr>
<tr>
<td>2.1 - 3.0</td>
<td>860</td>
<td>10.7</td>
</tr>
<tr>
<td>1.1 - 2.0</td>
<td>2472</td>
<td>30.8</td>
</tr>
<tr>
<td>0 - 1.0</td>
<td>3259</td>
<td>40.6</td>
</tr>
</tbody>
</table>
For clinical purposes, PSA is considered prostate organ specific but not prostate cancer specific

- Low concentrations of PSA have been identified in urethral glands, endometrium, normal breast tissue, breast milk, salivary gland tissue, and in the urine of males and females. PSA is also found in the serum of women with breast, lung, or uterine cancer and in some patients with renal cancer.
- Major limitation of PSA as a prostate cancer marker is the overlap in values between BPH and prostate cancer.

- Normal hyperplastic and neoplastic epithelial cells make PSA.
  - PSA produced by cancer cells is 10 times higher per gram of tissue than that produced by normal or hyperplastic tissue.
<table>
<thead>
<tr>
<th>Factors Influencing PSA Levels</th>
<th>Factors increasing PSA-levels</th>
<th>Factors decreasing PSA-levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prostatitis</td>
<td>Surgical castration</td>
</tr>
<tr>
<td></td>
<td>Benign prostatic hyperplasia (BPH)</td>
<td>LHRH-agonist antiandrogen therapy</td>
</tr>
<tr>
<td></td>
<td>Prostate cancer</td>
<td>Antiandrogen therapy</td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td>5-alpha reductase inhibitors (by 50%)</td>
</tr>
<tr>
<td></td>
<td>Ejaculation (by 40%)</td>
<td>PC SPES (herbal compound)</td>
</tr>
<tr>
<td></td>
<td>Digital rectal examination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate biopsy (by up to 650%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cystoscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other medication</td>
<td>Other medication</td>
</tr>
</tbody>
</table>
5-alpha reductase inhibitors such as finasteride (Proscar) and dutasteride (Avodart) decrease PSA levels by 50% in most men with BPH after a 6-month course of therapy 

*after which the level remains stable.*
Various herbal medicines may affect PSA as well.

Saw palmetto (Serenoa repens), frequently taken for “prostate conditions,” has been suggested to inhibit 5-alpha reductase, but in one large randomized trial, no impact on PSA was noted.
An increase in PSA levels occurs following ejaculation.

In 67% of the men older than 50 years who were tested, a 41% mean increase (0.8 ng/mL) in PSA occurred 1 hour after ejaculation.

PSA should be taken after abstinence for 48 hours.
PSA levels are elevated in acute prostatitis, chronic prostatitis, and urinary retention.

Nadler et al (1995) reported that serum PSA levels higher than 4.0 in 148 men with subclinical prostatitis could be attributed to their disease because all had negative findings from biopsies repeated on multiple occasions.
No significant change occurs in the PSA level following a DRE

Short-term 2-fold increase can occur if a vigorous prostate massage is performed

Cystoscopy, urethral catheterization, and transrectal prostate ultrasonography do not tend to elevate the PSA.

Performing a prostate needle biopsy increases PSA by a median of 7.9 ng/mL or 6.5 times baseline values within 5 minutes following the biopsy, and this level persists for 24 hours
- PSA testing in patients with normal serum PSA levels, defined as 4.0 ng/mL or less
  - Sensitivity of about 67.5% to 80%.
  - Specificity of about 60% to 70%.

- How to improve on this?
Men with prostate cancer had more complexed prostate-specific antigen (cPSA) than fPSA, in contrast to men with BPH.

The ratio of free-to-total prostate-specific antigen (f/tPSA) was lower in men with prostate cancer.

In the PSA range of 4-10, the f/tPSA is more discriminatory.
PSA velocity

- At least 3 PSA measurements are needed during a 2-year period or at least 12-18 months apart to obtain maximal benefit from the results.

- A PSA-V of 0.75 ng/mL or greater per year was suggestive of cancer \(\rightarrow 72\%\) sensitivity, 95\% specificity
Age-specific reference ranges

- Standard PSA reference range of 0.0-4.0 ng/mL does not account for age-related volume changes in the prostate.

- Overall specificity of 95%.
When is a prostate biopsy indicated?

- A urologist should be consulted for a prostate biopsy when any of the following findings are present:
  - PSA is 4.0 ng/mL or more;
  - A significant PSA rise from one test to the next; or
  - DRE is abnormal.
Other uses

- Determine Responses to Primary Therapy
- Early Detection of Recurrent PCa
- Monitor Responses to Hormonal Therapy
- Assess Responses to Therapy in Androgen-Independent PCa
The decision to use PSA for the early detection of prostate cancer should be individualized. Patients should be informed of the known risks and the potential benefits.

*Lifetime risk of dying from prostate cancer = 3%,
Lifetime risk of detecting prostate cancer by screening = 17%.*
Early detection of prostate cancer should be offered to asymptomatic men 50 years of age or older with an estimated life expectancy of more than 10 years.

It is reasonable to offer testing at an earlier age to men with defined risk factors, including men with a first-degree relative who has prostate cancer.
SUMMARY

- PSA is not a tumour marker
- Screening for Prostate Cancer with PSA is still controversial
- Individualised screening should be offered to men 50 years or older with life expectancy of >10 years
- Reference range is 0 – 4 ng/ml
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