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PEARLS OF LABORATORY MEDICINE

Prostate Specific Antigen (PSA): the Controversial Tumor Marker

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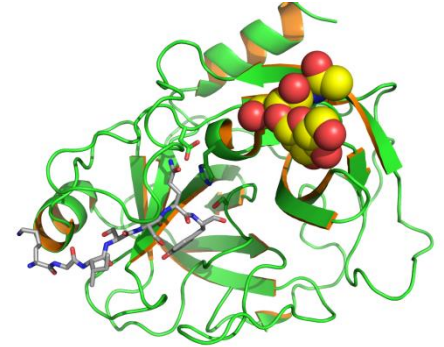
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Prostate Specific Antigen (PSA)

- Prostate cancer screening
- Serine proteinase
- Single-chain glycoprotein
- Four carbohydrate side chains (7% carbohydrate)
- Molecular weight = 28 KDa
- Isoelectric points = 6.8 to 7.2



Prevalence of Prostate Cancer

- The #1 cancer in men (28%) in US
- New cases: est. 238,590 in 2013
- Lifetime risk: 16.15% (1 in 6 men)
- Five-year relative survival rate: 100%
(based on 2002-2008 data)

Major Risk Factors

➤ Age

- Rare before 40
- Develops in 65% of men over 65

➤ Race

- High in African Americans; low in Asian-Americans
 - Often diagnosed at advanced stage
 - 2X more likely to die of the disease

➤ Family history

- First-degree relatives

PSA Clinical Applications

- Screening: Widespread use (since 1990s)
- Diagnosis: Limited
- Prognosis: Limited
- Monitoring recurrence: In use (FDA approved)

Screening

- NO specific PSA cutoff distinguishing cancer from non-cancer
- Traditional cutoff = 4.0 ng/mL

Cut-off	Sensitivity	Specificity	PPV	NPV
2.8	92%	23%	12%	96%
4.0	78%	33%	11%	93%
8.0	39%	90%	30%	93%
20.0	23%	100%	100%	92%

Assumptions:
Population: Men > 50 years old
Prevalence = 10%

Approaches to Increase Specificity

- PSA Density
 - Normalized to prostate volume
- PSA Velocity
 - Change in PSA over time (e.g., more than 15% per year)
- Free PSA/Total PSA Ratio
 - Lower ratios suggest cancer, since more free PSA from normal prostate (< 10% → biopsy)

European Randomized Study of Screening for Prostate Cancer (ERSPC)

➤ Study Design

- 182,160 men ages 50 – 74
- Eight European countries
- 11-year follow-up
- Primary outcome: mortality

➤ Results

- Relative reduction in the risk of death = 21%.
- Absolute reduction in mortality = 0.10 deaths per 1000 persons/year
- To prevent one death from prostate cancer:
 - 1055 men need to be invited for screening
 - 37 cancers need to be detected
- Screening did not show effect on all-cause mortality.
- The effect on quality of life is pending.

Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)

➤ Study Design

- 76,685 men ages 55 – 74
- Ten screening sites
- 13-year follow-up
- Primary outcome: mortality

➤ Results

- Cumulative incidence rate: 108.4 (intervention) vs. 97.1 (control) per 10,000 persons/year
- Cumulative mortality rate: 3.7 (intervention) vs. 3.4 (control) per 10,000 persons/year
- No evidence of a mortality benefit for organized annual screening

U.S. Preventative Services Task Force

➤ Study Design

- MEDLINE (2002 – July 2011) and Cochrane Library Database (through second quarter of 2011)
- Study Selection
 - Randomized clinical trials of PSA screening
 - Randomized trials and cohort studies of prostatectomy or radiation therapy vs. watchful waiting
 - Large observational studies of perioperative harms

➤ Conclusions

- Recommend against PSA screening
- PSA-based screening:
 - Showed small to no reduction in prostate cancer-specific mortality
 - Associated with harms from subsequent evaluation & treatments

Arguments For and Against Screening

For Screening

- Health burden and prevalence
- High sensitivity/
Negative predictive value
- Some studies show decreased mortality from screening

Against Screening

- High false-positive rate
- No or little evidence to show benefit of screening for mortality from large-scale randomized trials
- Cost

Analytical Perspective: PSA Standardization

- Hybritech (now Beckman Coulter)
- World Health Organization (WHO)
- Hybritech is ~ 20% higher than WHO

Summary

- Screening of prostate cancer using PSA remains controversial
- Many new biomarkers are in development to increase specificity for prostate cancer screening

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