Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Prostate Specific Antigen: The Controversial Tumor Marker

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Slide 1: Introduction

Hello, my name is Yan Zhang, an Assistant Professor in the Department of Pathology and Laboratory Medicine at the University of Rochester Medical Center and Associate Director of Clinical Chemistry and Toxicology Laboratories at Strong Memorial Hospital. Welcome to this Pearl of Laboratory Medicine on "Prostate Specific Antigen: The Controversial Tumor Marker."

Slide 2: Prostate Specific Antigen (PSA)

Prostate specific antigen (PSA) has been used extensively for prostate cancer screening since 1988. It is a serine proteinase that has four carbohydrate side chains, which account for about 7% of its total molecular weight. PSA is also a single-change glycoprotein composed of 237 amino acids with a molecular weight of about 28 KDa. Its isoelectric points vary from 6.8 to 7.2 due to various components of the carbohydrate side chains.

Slide 3: Prevalence of Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of cancer death in the male population. It accounts for about 28% of total cancer incidences and 10% of total death. The estimated new cases were 238,590 based on the 2013 cancer statistics report. The lifetime probability of developing invasive prostate cancer is 16.15% or one in six men. Men age 70 and older have the highest probability of developing invasive prostate cancer with a rate of 12.06% or one in eight men.

In comparison to other cancer types, prostate cancer is a slow-growing cancer with a relatively high survival rate. Based on patients diagnosed with prostate cancer between 2002 and 2008, the five-year relative survival rate was 100%. This is a significant improvement from 1977 and 1989 when survival rates were 68% and 83%, respectively.

Slide 4: Major Risk Factors for Prostate Cancer

The major risk factors for prostate cancer include age, race, and family history. Prostate cancer is rarely found in men before the age of 40, while about 65% of men age 65 and older have some level of prostate cancer.

It has been shown that prostate cancer has a higher prevalence among African-American men, but is less frequently found in Asian-Americans. For African-American men, prostate cancer is more often diagnosed at an advanced stage and they are two times more likely to die from the disease than the general population.

Men with first-degree relatives who had prostate cancer will also have a higher likelihood of developing the disease.

Slide 5: Clinical Applications in Prostate Cancer

PSA has four major clinical applications in prostate cancer. The most widespread usage is for prostate cancer screening, which was introduced in the 1970s and became popular in the 1990s. PSA has been shown to have limited usage for the diagnosis and prognosis of prostate cancer; however, PSA levels have been widely used for monitoring disease treatment and the recurrence of prostate cancer.

Despite its use for cancer diagnosis since 1988, the value of PSA as a screening tool remains controversial. This has led to conflicting recommendations regarding the use of PSA as a screening tool. This presentation will therefore place particular emphasis on evaluating the screening value of PSA.

Slide 6: Screening

PSA has been widely used for prostate cancer screening. It's important to know that there is NO specific PSA cutoff to distinguish cancer from non-cancer due to the significant overlap of PSA levels between disease and control groups. However, the higher the PSA level in a man, the more likely he will have prostate cancer.

The typical cutoff for PSA is 4.0 ng/mL. The table below shows the sensitivity, specificity, and positive and negative predictive values at different PSA cutoffs. The target population is men over the age of 50 and the assumed prevalence is 10%.

At the typical cutoff of 4.0 ng/mL, the sensitivity is 78% and the specificity is only 33%, which results in an 11% positive predictive value and a 93% negative predictive value. In other words, a cutoff of 4.0 ng/mL can produce a significant number of false positive results.

As the PSA cutoff increases, the specificity increases from 23 to 33, and to 90%. To reach the specificity of 100%, the PSA cutoff needs to be as high as 20ng/mL, which will only give 23% sensitivity. The negative and positive predictive values change accordingly, although the negative predictive values decrease in a less significant fashion from 96% to 92% due to the high prevalence of prostate cancer.

It's important to mention that an elevated PSA can result from benign prostate hyperplasia and prostatitis, and that PSA levels are also affected by age and ejaculation.

Slide 7: Approaches to Increase Specificity

Studies have been done to find new markers to improve the specificity of PSA in prostate cancer screening which include PSA density, PSA velocity, and free PSA to total PSA ratio. PSA density is to

normalize PSA concentration to prostate volume. PSA velocity is to calculate the PSA concentration change over time. A more than 15% change per year indicates a worse prognosis. Studies have shown the utility of free versus total PSA ratio. As more free PSA are produced from normal prostates, lower ratios suggest cancer. A ratio of 10% suggests the need for a biopsy follow-up.

There is no question that these new developments in PSA screening can help detect many prostate cancers at an early stage, but they each have limitations resulting from inaccurate testing. The high false-positive rate from such tests can lead many men to have a prostate biopsy when it is not necessary. Any biopsy may lead to side effects such as pain, infection, and bleeding. On the other hand, false-negative test results can give some men a false sense of security when they may actually have cancer.

Another issue is that even if screening detects cancer, the results do not necessarily help doctors to determine the severity of the cancer or to tell if the cancer is truly life-threatening. It is a conventional belief that the earlier the diagnosis and treatment take place, the better the outcome would be. However, some prostate cancers are very slow growing and most patients would probably never even develop any symptoms, let alone die from the cancer.

On the other hand, treatments like surgery and radiation can have serious side effects such as urinary, bowel, and/or sexual issues that may have a significant negative impact on a man's quality of life.

Screening with PSA for prostate cancer seems to be a double-edged sword. The arguments have been focused on the cost and benefit of screening within the larger population, particularly the mortality or survival benefit of early detection of prostate cancer using PSA. The most recent results from two large randomized clinical trials have drawn significant attention to the need for further discussion of the utilities of PSA screening.

Slide 8: ERSPC Trial

There has been a lot of discussion about the benefits of prostate cancer universal screening using PSA, especially after the publication of two large randomized clinical trials: the ERSPC trial from Europe and the PLCO trial from the US.

This slide summarizes the ERSPC or the European Randomized Study of Screening for Prostate Cancer. The study had 182,160 men enrolled between the ages of 50 and 74, with eight European countries participating. The report was produced after 11 years of follow-up with a special focus on mortality from prostate cancer as the primary outcome.

The study found that screening provided a 21% relative reduction in the risk of death and 0.1 deaths per 1000 persons/year absolute reduction in mortality. The study also found that in order to prevent one death from prostate cancer, 1055 men needed to be invited for screening and 37 cancers needed to be detected. Despite the prostate-specific risk reduction, the ERSPC study indicated that screening using PSA did not show a statistically significant effect on all-cause mortality. Further analysis is in process to assess the impact of PSA screening on quality of life.

Slide 9: PLCO Trial

The PLCO or randomized Prostate, Lung, Colorectal, and Ovarian Cancer screening trial took place in the United States and had 76,685 men between the ages of 55 and 74 enrolled at 10 screening sites. The follow-up time was 13 years from the most current report in 2011, which used mortality as the primary outcome.

The key findings of the study include the cumulative incidence rate of 108.4 per 10,000 persons/year in the intervention group and 97.1 in the control group. The cumulative mortality rates per 10,000 persons/year in the intervention and control groups were 3.7 and 3.4, respectively. The study concluded that there was no evidence of a mortality benefit for organized annual screening of PSA for prostate cancer.

Slide 10: U.S. Preventative Services Task Force

ERSPC and PLCO presented contradictory results regarding benefit of PSA screening for prostate cancer.

The U.S. Preventive Services Task Force (USPSTF) undertook an additional study to analyze the impact of PSA screening. The task force reviewed studies listed in MEDLINE from 2002 to July 2011 and the Cochrane Library Database through the second quarter of 2011. These studies included randomized clinical trials of PSA screenings such as the two large randomized trials indicated above, randomized trials and cohort studies of prostatectomy or radiation therapy versus watchful waiting, and large observational studies of perioperative harms.

After analyzing all the information, USPSTF recommended against PSA screening due to the fact that PSA screening showed small to no reduction in prostate cancer-specific mortality. Moreover, it found that PSA screening is associated with harms from the subsequent evaluation and treatments.

Slide 11: Reasons For or Against Screening

Organizations such as the U.S. Preventive Services Task Force recommend against prostate cancer screening using PSA, while groups such as the American Urological Association support PSA screening. The discrepancy lies in the different focuses of the studies. Different arguments have been made by each side.

The reasons cited for screening include the significant health burden of prostate cancer and its prevalence in men. PSA screening has relatively high sensitivity, which leads to over 90% negative predictive value. In addition, some studies have shown decreased mortality from screening.

On the other hand, the arguments made against screening include the high false positive rate and low specificity of PSA. So far, based on the two large randomized clinical trials, little to no evidence has been found to demonstrate the benefit of screening for mortality. In addition, the cost of general screening will add significant financial burden to the health care system.

Slide 12: Analytical Perspectives: PSA Standardization

PSA testing was originally developed by Hybritech, which is now owned by Beckman Coulter. The World Health Organization (WHO) also published standards for PSA testing. Due to different antibodies and affinity, the Hybritech method is generally 20% higher than the WHO method. Cautions should be taken when interpreting results from different platforms.

Slide 13: Summary

Screening of prostate cancer using PSA remains controversial. The key issue remains high false positive rates. Many new markers are in development to increase specificity to improve the positive predictive value of laboratory tests for prostate cancer screening.

Slide 14: References

Slide 15: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "Prostate Specific Antigen: The Controversial Tumor Marker." I am Yan Zhang.