MAYO CLINIC

EDITORIAL

January 2013
Volume 88
Number 1

MAYO CLINIC
PROCEEDINGS

PSA: Please Stop Agonizing* (Over Prostate-Specific Antigen Interpretation)

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The introduction of measurement of prostate-specific antigen (PSA) into the algorithms for managing prostate cancer has been a mixed blessing. There is no doubt that the preliminary work on prostatic proteins by multiple investigators (carefully refined by T.M. Chu and his group,[1] leading to the study and application of PSA as we know it today) has provided a useful tool for the characterization and management of prostatic diseases. Prostate-specific antigen is a relatively specific protein that is associated with prostatic disorders, both benign and malignant, and generally correlates well with the existence of many abnormalities of the prostate.[1] Clearly, it is associated with benign prostatic hyperplasia (BPH), and usually the PSA level increases to reflect the volume of BPH. In addition, PSA is produced by malignant prostate tissues and often correlates with extent of disease and tumor progression. One of its limitations is that poorly differentiated prostate cancers often are PSA silent, or occasionally there is a discrepancy between the volume or bulk of tumor and the amplitude of PSA production (with apparently modest levels of PSA, suggesting the presence of lower tumor bulk than is actually present). With these limitations in mind, PSA has come to be a useful tool in the management of advanced prostate cancer, both as a parameter of early tumor response to treatment and sometimes as a prognostic determinant.[2,3] More recently, evidence has suggested that the measurement of circulating tumor cells may displace PSA as the most useful prognostic indicator,[4] but this remains to be proven.

What about the use of PSA to screen for early-stage prostate cancer? Many of my friends in the world of urology love this little protein[5,6] because they believe that it helps them follow up patients with a defined marker, allows the documentation of early relapse after definitive surgery or radiotherapy, encourages patients to return regularly for follow-up (with something to discuss after each visit), and enhances the development of a series of prognostic tools and algorithms for use in early-stage disease (most of which have severe limitations of sensitivity and specificity). One could argue that, on the basis of these principles, a PSA-associated growth industry has emerged, with a goal of screening immense numbers of patients for early-stage prostate cancer.[6] This remains a domain of extreme vexation to clinicians and patients, largely because nobody seems able to agree on the interpretation of extant data. Many of the urologic associations and some patient advocacy groups have taken the following stance:

- Screening allows early detection of many cancers and thus saves lives.
- Regular PSA checks lead to early diagnosis and early treatment and thus should save lives.
- The proportion of patients with an earlier stage of disease at diagnosis is much higher today because of PSA-associated diagnosis programs.
- The proportion of patients who die of prostate cancer has decreased in the past 2 decades.
- Some randomized trials, comparing screened and unscreened control populations, have demonstrated reduction of deaths from prostate cancer or prolongation of disease-free interval in the screened arms.[7-9]
- Many of the randomized trials that have not shown benefit were heavily flawed in design or execution.[10]
- Thus, screening with PSA, perhaps amplified by digital rectal examination, must be a good thing.

The contrasting view, perhaps espoused most visibly by the US Preventive Services Task Force (USPSTF),[11] is as follows:

- There is no randomized clinical trial that has reported *overall* lives being saved by PSA or equivalent screening programs.[7-10]
- Some of the published randomized trials have actually reported a deficit in survival among some of the screened populations (eg, older-aged cohorts).[10]
- Most published data have not found a real population benefit from current prostate screening algorithms.
- As a result, the USPSTF has recommended against routine prostate screening strategies that are based on the currently available tools.[11]

Predictably this has led to confusion and an outcry from the first lobby group, with the expressed concern that lives will be lost because of this stance.[12] As I see it, the following important points apply:

- Prostate cancer is a remarkably heterogeneous disease, and there clearly is a subtype that will coexist in elderly men for many years, which poses no threat to their longevity or lifestyles unless disrupted by the consequences of aggressive postscreening treatment algorithms.
- We need to educate men about the existence of prostate cancer, its symptoms and presentations, the availability of treatment, and key facts relating to the debate about screening.
- We should be educating some of our clinical colleagues about the difference between population-based PSA screening and the use of PSA in assisting in the diagnosis and management of a male with urinary tract symptoms.
- In tumors for which screening is of unequivocally proven benefit (eg, mammography for breast cancer and colonoscopy for colon cancer), there is a stage shift at presentation, an increment in disease-specific survival, and, most importantly, a significant and clinically relevant increment in *overall* survival; this has never been shown in the randomized trials of prostate screening, despite lengthy follow-up.
- Cancer-specific death rates, in isolation, do not provide sufficient benefit to support routine population-based screening because they may well mask an increment of morbidity or mortality in other areas (eg, the consequences of hormonal manipulation or the complications of surgery).
- The absolute numbers of deaths from prostate cancer each year in the United States, since the introduction of widespread prostate screening, has not decreased as notably as implied by much of the rhetoric in support of this program—25,943 deaths from prostate cancer in 1989[13] and 28,170 deaths from prostate cancer in 2011[14]; what has changed rapidly is the denominator of cases, implying the discovery of a large reservoir of incidental cases.
- The USPSTF made its decision on the basis of studies that did not address, in any meaningful way, African Americans or men with family histories of prostate cancer; if they had ab initio formally addressed the professional organizations that provide care to this population of patients, they might have framed their recommendations more accurately; responsible clinicians need to be particularly careful in framing their discussions on screening for these 2 groups.

So what of the interesting article in this issue of *Mayo Clinic Proceedings*[15] by Loprinzi and Kohli? They have had the enterprising thought of reviewing the results of the National Health and Nutrition Examination Survey to correlate physical activity and PSA measurement as a potential surrogate to demonstrate a link between the lifestyle of the couch potato and the genesis of prostate cancer. As presented, the data are compelling and may well indicate an accurate linkage between inactivity and the genesis of prostate cancer. There is an emerging body of literature to support links between obesity and cancer. This study could provide further mechanistic support for this concept.

However, important caveats should also be considered, including the potential for case selection bias (especially because this study reflects less than 20% of the patients participating in the National Health and Nutrition Examination Survey) and the important consideration that elevated PSA may simply indicate the presence of larger than normal amounts of some type of prostate tissue (including BPH) and not purely restricted to

Mayo Clin Proc. ■ January 2013;88(1):1-3 ■ http://dx.doi.org/10.1016/j.mayocp.2012.11.004
www.mayoclinicproceedings.org

cancer (particularly in the levels identified in this study). Thus, it is conceivable that their study suggests a link between lack of exercise and BPH. Further work in this area, as suggested by the authors, is clearly indicated.

The important message of this study is that we should be focusing on the *genesis* of this cancer because it has become an important demographic and epidemiologic challenge. Toward this goal, these types of large and expensive surveys should be used more efficiently to cover a broad range of targets.

We also need to apply PSA in its full context, moving rhetoric to the side, and attempt to implement thoughtfully designed and well-structured, hypothesis-driven studies to reveal ways to diagnose the more dangerous prostate cancer variants earlier, or prevent them from occurring, and to develop better management paradigms for those who present with advanced disease. International data suggest that there is a new epidemic of prostate cancer among urban Chinese, Koreans, and Japanese, domiciled in their homelands or in Western nations,[16] and this may present an opportunity for further field testing of some of the strategies enumerated in this editorial at a sufficiently early time to have a real population-based effect.

ACKNOWLEDGMENTS

*The phrase in the title "PSA - Please Stop Agonizing" is drawn from a conversation with Lawrence Einhorn MD, Indiana University, some years ago.

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