Written Testimony to the House Oversight Committee and Government Reform

March 4, 2010

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Prostate-Specific Antigen (PSA) for Early Detection of Curable Prostate Cancer

Two studies in the March 26, 2009 issue of the New England Journal of Medicine re-ignited the debate about the value of PSA screening. The American study[1] reported no survival benefit with a median follow-up of 11 years where 2/3 of men had been followed at least 10 years. The European study[2] reported a 20% reduction in deaths from prostate cancer with median follow-up 9 years.

What should men take away from these studies? First, publication of these studies appears premature. Men with PSA detected prostate cancer have a mean life expectancy without treatment of 23 years. Thus, most men in both studies have not yet had an opportunity to suffer a death from prostate cancer. Second, the European study is probably a better test of PSA for early detection. However, PSA screening there was offered only once every 4 years. The US study conformed more to the usual recommendations of an annual PSA that was delivered in the screening group for 6 years and 85% of men underwent screening. However, in the control group that was not to be screened, 52% of men had had a digital rectal exam or PSA in the last year. In addition, 44% of men in both groups had already had a PSA and digital rectal exam prior to enrolling in the study. Thus, one could interpret the American study to be a test of regular screening versus almost regular screening. In Europe, the medical community, specifically, and men, in general, are more skeptical about the use of PSA for early detection. Hence, very few members of the control group probably underwent screening although this information was not collected. Hence, the European Study control group probably more closely resembles an unscreened group, although the screened group had only a PSA every 4 years which may not be the best detection strategy for prostate cancer. A follow-up period of an additional 5 and probably 10 years will be necessary to properly evaluate whether PSA has value for early detection of prostate cancer.

In the meantime, what should men do? PSA performs best if it is used for “early detection” not “screening.” PSA should not be used as a screening test. A “screening” test would measure PSA in the entire population. One would not test women, boys, or elderly men in poor health.

PSA performs better when used for "early detection." In order for PSA to perform best, it should be used in populations at increased risk for prostate cancer. That population is those men who are African American[3] or have a father or brother with prostate cancer.[4,5] Unfortunately, the European Study did not address race and less than 5% of research subjects in the American Study were African Americans. Less than 7% of the men in the American study had a family history of prostate cancer and the extent of that history appears not to have been defined. Thus, at this time, men should follow the recommendations of the American Cancer Society, the American Urological Association, and the National Comprehensive Cancer Network and await the maturation of these two important studies.

In the meantime what should men not do? We need not return to the pre-PSA era. In the early 1980's, most men presented with symptomatic prostate cancer that was metastatic and hence incurable and average survival was 3 years. Only 4% of men were found to have clinically localized prostate cancer and hence were candidates for curative therapy. Today, less than 10% of men present with advanced prostate cancer. More than 90% of men are candidates for curative therapy and 5 year survival rates approach 100%. The evidence that too many prostate cancers are diagnosed is clear. Today, 1 in 6 American men will be diagnosed with prostate cancer but only 1 in 25 will die of prostate cancer. Prostate cancer can be diagnosed by subjecting all men to annual PSA tests and treating anyone in whom we can diagnosis prostate cancer. However, the chance of an American man having prostate cancer is about the same as his age if his prostate was removed and autopsied.[6-8] If 12 needle biopsies of the prostate are performed, about 50% of "autopsy" prostate cancers will be found.[9] Clearly we do not want to diagnose prostate cancer in every man in whom it can be diagnosed. What we want to do is to diagnose prostate cancer in every man who is destined to die from prostate cancer unless it was diagnosed early and treated appropriately. Unfortunately, we lack the tools to assess the aggressiveness of prostate cancer - we need a "fingerprint" of the aggressive phenotype of prostate cancer. Until that time, we must rely on careful use of guidelines to select men appropriately for biopsy and, among those found to have prostate cancer, select them appropriately for treatment. PSA performs much better as an early detection test for prostate cancer when it is used more aggressively in younger men to detect those at higher risk of prostate cancer death. The performance of PSA deteriorates when it is applied indiscriminately to men and used as a screening test. Hence the NCCN and other prostate cancer early detection guidelines have responded to recommend that routine PSA testing end when life expectancy falls to <10 years. The NCCN guidelines (http://www.nccn.org/professionals/physician_gls/PDF/prostate_detection.pdf) recommend that younger men be early detected more aggressively – PSA should be performed more often in men with PSA >1.0 at age 40 and less often as a man has a normal PSA level and becomes older. Men who are African American or have a family history of prostate cancer should adhere carefully to recommendations for prostate cancer early detection.

Prostate Cancer is More Common and More Often Fatal in African Americans

An American man is diagnosed with prostate cancer every 3 minutes and dies from the disease every 17 minutes[10] and the worldwide autopsy of prostate cancer is increasing an estimated 1.1% annually.[11] Although the frequency of incidental prostate cancer is similar between races,[7,8] African Americans have a higher incidence of, and greater mortality from, prostate cancer than Caucasian Americans. In fact, African Americans have the highest incidence and mortality rates

of prostate cancer in the world. Difference in prostate cancer incidence between men of different geographic origin is not unique to the United States; for example, in Sao Paulo, Brazil, prostate cancer is 1.8 times more common in Brazilians of African than European origin.[12]

Data from the SEER database (1993-1997) show that the incidence of invasive prostate cancer is greater in African Americans than Caucasian Americans: 1.9 times greater in men <65 years of age and 1.6 times greater in men ≥65 years of age.[13] In men <65 years of age, the prostate cancer mortality rate for African Americans is 3.1 times that of Caucasian Americans. In men ≥65 years of age, the prostate cancer mortality rate for African Americans is 2.3 times that of Caucasian Americans.[13] These data suggest that there is no racial difference in the development of prostate cancer (initiation), but clinical prostate cancer develops (progression) more frequently in African Americans than Caucasian Americans and, once prostate cancer presents clinically, prostate cancer is more lethal in African Americans than Caucasian Americans (reviewed in reference 14).

The racial differences in participation in prostate cancer early detection programs are narrowing. However, racial differences persist in interaction with the health care system. Many of these differences may be more socioeconomic than racial but many African Americans lack trust in the American health care system that may be overcome by personal interaction with their health care provider. African Americans more often use alternative medicines and may more frequently decline potentially curative treatments. Racial differences in host and tumor biology are difficult to evaluate. African Americans more often consume higher fat diets and are more often obese, both of which may promote prostate carcinogenesis. Although there is no evidence for higher serum androgen levels in African Americans compared to Caucasian Americans, their prostates may be more sensitive to androgens due to a shortened CAG repeat within the androgen receptor gene. Studies involving hereditary prostate cancer and genetic polymorphisms that may affect prostate cancer risk have frequently not included high numbers of African Americans and the interpretation of such studies are further complicated by issues regarding population stratification. Although there are no racial differences in PSA and its derivatives, African-American prostate cancer may have higher tissue levels of sex hormone binding globulin (SHBG) and increased androgen receptor protein expression.[15] Although some studies suggest racial differences in growth factors and cell regulatory pathways, these studies require studies of larger numbers of men.

Study of all aspects of this important health care problem has accelerated rapidly in the past decade. The number of citations in PubMed on prostate cancer and African Americans has increased from 65 in 1994 to 207 in 1999 to 405 in 2004 and to 1,115 in 2009. The National Cancer Institute, American Cancer Society, and Department of Defense Prostate Cancer Research Program have given high priority to research proposals that address prostate cancer racial disparities. Thoughtful discussions about the definitions of race,[16,17] the usefulness of race in genomics[18,19] and medicine[20] and "whether socioeconomic conditions represent a more pertinent cause of [health care] disparities than race" have begun.[21-23]

One such effort is the North Carolina-Louisiana Prostate Cancer Project (PCaP), which is funded by the Department of Defense Prostate Cancer Research Program and officially titled, "Racial differences in prostate cancer: Influences of health care interaction and host and tumor biology."

PCaP is in its 7th year of funding, which concludes October 2010; the total award has reached $15.2M. The proposed research attempts to categorize the reasons for racial disparity in prostate cancer mortality on three levels: racial differences in the quality of patient interaction with the health care system, racial differences in the biological characteristics of the host, and racial differences that may exist in the biology of the prostate cancers. Successful completion of these studies should allow more intelligent allocation of resources to reduce the burden posed by prostate cancer in all men and especially African Americans.

Rapid case ascertainment was used to identify a total of 2264 research subjects (similar numbers of African and Caucasian Americans) with newly diagnosed prostate cancer from North Carolina or Louisiana (1/2 from each state) and the last home visit was September 8, 2009 in Louisiana. All men were home visited and interviewed with information collected regarding knowledge of prostate cancer, early detection behavior, health care attitudes, beliefs, and experiences, diet and exercise, family history, race and ethnicity, and medical history. Biological specimens were collected that include toe nails for heavy metal exposure, adipose tissue for dietary exposure, blood for plasma and serum dietary exposure, DNA and RNA isolation, urine for heavy metal and pesticide exposure, prostate biopsy tissue sections for growth rate, androgen-regulated gene expression and prostate stem cell count, and radical prostatectomies (where performed) for tissue microarray construction. Careful abstraction of medical records yielded diagnostic PSA, and clinical and pathological grade and stage from which clinical tumor aggressiveness was assigned. PCaP specimens are made more valuable by complete clinical annotation and outcome collected for both the North Carolina and Louisiana study populations under two grants from the American Cancer Society. In addition, mortality data is available for all research subjects through the North Carolina State Center for Health Statistics and the Louisiana State Tumor Registry. The PCaP data and biological specimens currently are under study by nine scientific projects and additional projects continue to be submitted for funding. The institutions comprising PCaP include Roswell Park Cancer Institute, University of North Carolina, Louisiana State University Health Sciences Center, Wake Forest University, Johns Hopkins University, Boston University, Harvard University, University of South Carolina, Duke University Medical Center, James Madison University, Louisiana State University at Baton Rouge and NIEHS.

PCaP was described in The Prostate[24] and has produced 4 additional publications.[25-28] The first publication from a scientific project appeared in Cancer, a high impact journal, and demonstrated that African-American men present with more aggressive prostate cancers than Caucasian-American men at least in part because they are less likely to see the same primary care provider and thus less likely to benefit from strategies to prevent the development of common chronic diseases or to early detect common cancers.[28] The PCaP biorepository of research specimens and their annotation with clinical data and outcome provides a valuable resource for interrogation by PCaP researchers and researchers from other institutions.

Prostate Cancer Treatment

Prostate cancer is a complex disease for which many aspects of management remain controversial. The primary reason for controversy is the lack of sound data to support most recommendations. Several variables must be considered to tailor prostate cancer therapy to an individual patient. Many believe that guidelines provide a framework to guide discussion with

patients and base treatment decisions. Proper decisions regarding prostate cancer treatment depend upon accurate assessment of tumor aggressiveness, which depends upon extent of disease (stage), histological differentiation (Gleason grade), absolute value of PSA, and rate of rise of PSA (PSA velocity or PSA doubling time). The incidence of prostate cancer increased following the wide adaption of PSA for screening/early detection in the late 1980s and since has stabilized and perhaps declined when age adjusted;[3] the incidence of prostate cancer increased 30% from 1994 to 2009. Every year since 1992 the death rate from prostate cancer has declined; the decline in prostate cancer mortality has now reached 36%.

Radical prostatectomy has been shown to extend survival in a randomized controlled trial of radical prostatectomies vs. expectant management.[29] Radical prostatectomy decreased the absolute risk for local progression by 25%, distant metastasis by 10%, and overall mortality by 5%. Men <65 years of age experienced a greater survival advantage but this was found in a statistically improper subset analysis. Most men were diagnosed before the PSA era so how these study results apply to men diagnosed today remains unclear. Finally, the overall decrease in mortality was 5% but that represented a reduction in overall mortality from only 14.9 to 9.6%.

If treatment had no morbidity, one could diagnosis prostate cancer in everyone in whom it could be diagnosed and treat everyone. Operative mortality has been reported as high as 0.5%, urinary incontinence occurs in 5-60% after radical prostatectomy and 8% after radiation therapy, and rates of impotence range as high as 56% after operation and 70% after radiation therapy.[30-33] Both operation and radiation are being refined technologically in an attempt to decrease the side effects of treatment while maintaining or improving oncologic outcome. Minimally invasive surgery is replacing open surgery largely as a result of patient preference for more rapid recovery of activities of daily living and urinary control although the long term side effects and oncologic outcomes from the 2 approaches seem similar.[34] Radiation therapy is being delivered to higher dose with greater safety due to the development of Intensity Modulated Radiation Therapy (IMRT) and the 2010 NCCN guideline requires image guided radiation therapy (IGRT) techniques whenever radiation dose exceeds 78 gray.

The American and European PSA early detection trials[1,2] have reignited a debate about overtreatment of prostate cancer. A large international trial (Observation or Radical Treatment in Patients With Prostate Cancer - Full Text View - ClinicalTrials.gov) is underway to investigate active surveillance vs. immediate treatment in men with low risk prostate cancer, which is based on a large cohort experience[35]. Dr. Lawrence Klotz has estimated that one must "treat an estimated 200 men with low risk prostate cancer in order to prevent 1 prostate cancer death." The European trial estimated 1,410 men would need to be screened and 48 additional cases of prostate cancer would require treatment to prevent 1 death from prostate cancer,[2] whereas the American trial detected no evidence of benefit to prostate cancer screening.[1] As the active surveillance experiences mature, more American men are being offered active surveillance. There seems to be little risk of prostate cancer converting from curable to incurable during a period of active surveillance that lasts 3 months,[36] 6 months,[37] or as long as 2 years.[38] Furthermore, Gleason score rarely changes between diagnosis and re-biopsy. The rate of histological progression varies between 2.4%[39] and 13%[40] but most agree that it is 4% or less.[39,41,42] The Toronto, Johns Hopkins, and University of California at San Francisco (UCSF) experiences are converging in spite of differences in patient selection, disease monitoring, and

criteria for disease progression. About 25% of men eventually undergo treatment and about 1/3 do so for anxiety not disease progression.

North American Active Surveillance Experience

Centers References	Toronto 35	Hopkins 43,44	UCSF 45
No. Patients	450	407	531
Age (yr)	70	66	63
F/U (mo)	82	41	43
OS	68%	98%	98%
CSS	97%	100%	100%
Treatment	30%	25%	24%
GS↑	8%	19%	38%
PSA	14% (DT<3 yrs)	-	16% / 26% (PSAV>0.75)
Nodule	1%	-	-
Anxiety	3%	7%	8%

The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 21 of the 40 NCI designated Comprehensive Cancer Centers, is dedicated to improving the quality and effectiveness of care provided to patients with cancer. The NCCN Clinical Practice Guidelines in Oncology™ are developed and updated through an evidence-based process with explicit review of the scientific evidence integrated with expert judgment by multidisciplinary panels of physicians from NCCN Member Institutions. The most recent version of this and all the NCCN Guidelines are available free of charge at http://www.NCCN.org. The NCCN Prostate Cancer Clinical Practice Guidelines were developed in 1995 and are updated annually.

The most significant change in the 2010 Prostate Cancer Clinical Practice Guidelines is the recommendation for active surveillance and only active surveillance for men with "low risk" prostate cancer who have life expectancy <10 years. In addition, a new "very low risk" category has been created using a modification of the Epstein criteria for clinically insignificant prostate cancer[46] where active surveillance is the only recommended option for men when life expectancy is <20 years. A new algorithm may select men even better for active surveillance. [47] These recommendations grow from 2 fundamentals appreciated by the guideline panel.

First, growing evidence suggests that overtreatment of prostate cancer commits too many men to side effects that outweigh a very small risk of prostate cancer death, an issue discussed by Klotz in JNCCN[42] that led to the first major modification of the NCCN prostate cancer treatment guidelines regarding active surveillance in 2009. Second, the continued maturation of experience by many medical centers with large series of men on active surveillance allows better recognition of men for whom risk of death from prostate is very low.

The 2010 Guideline panel recognizes the difficulty of predicting the future of individual patients, but feels strongly that continued treatment of all men in whom prostate cancer can be diagnosed is as wrong as denying treatment to every man in whom prostate cancer is diagnosed. Best practice lies in between these two extremes.

Recommendations

1. Blood (or urine) tests that can be combined with PSA to indicate who doesn't need a prostate biopsy so that men with autopsy-type prostate cancer can be spared biopsy and the anxiety attached to a diagnosis of prostate cancer.
2. A tissue-based biomarker of life-threatening prostate cancer. Currently, PSA, extent of disease, and Gleason grade of cancer correlate with prostate cancer aggressiveness in groups of patients, but not individual patients. More funds must be spent to develop biomarkers of aggressive prostate cancer and I believe that may come through more careful study of the prostate cancers found in African Americans.
3. Until recommendations 1 and 2 are met, NCCN guidelines should be used to guide the diagnosis and treatment of prostate cancer to assure that the mortality from prostate cancer continues to decline while not subjecting men to the consequences of overtreatment of prostate cancer.

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