

To treat or not to treat, that is the question

By Paul F. Schellhammer, M.D.

An article in the Journal of the National Cancer Institute appeared in July that raised a number of unsettling questions and issues for patients recently diagnosed with prostate cancer who are considering treatment as well as patients who have already been treated. The thrust of the study was that fully a third of patients diagnosed with prostate cancer did not require therapy. These patients, therefore, would suffer the inconvenience, expense, side effects, and emotional upheaval that are part and parcel of a cancer diagnosis and subsequent treatment. The article puts in clearly defined mathematical data a fact that is recognized by urologists and also by patients who have had a discussion with their physician about the diagnosis of prostate cancer. As has been frequently stated, prostate cancer is a disease of aging. Careful autopsy studies of younger men in their 30s and 40s suffering traumatic death has revealed a 20-30% incidence of early microscopic prostate cancer, and similar studies in aged men in their eighth decade have revealed this incidence at 70-80%. Clearly not 70-80% of men, not even 20-30% of men die of prostate cancer. (These figures may become an issue if life can be extended well beyond the century mark). Therefore, physicians involved in the diagnosis and treatment of prostate cancer have to use good judgment and provide rational

information to patients to include but not limited to the following guidelines:

- Men over the age of 75, certainly if they have other illnesses, in the absence of any physical findings or symptoms may choose to omit PSA testing. They do have a 70% chance of

having prostate cancer (we know that), but its threat to their life and health is miniscule, and treatment could render significant complications. Often the treatment is more dangerous than the disease.

- Men over the age of 70, with marginally elevated PSAs, can consider observation with serial PSA readings as an alternative to prompt biopsy.
- Men with significant other medical illnesses, for instance severe diabetes, renal failure, or cardiac failure should, regardless of age, discuss the wisdom of biopsy with their physicians.
- If a biopsy is performed and is positive for cancer, a number of factors need to be considered; namely the Gleason score or the grade of the cancer, the number of cores that are positive, the extent of tumor in the positive cores (i.e. <10% vs >90%).

As an example, a 72 year old male who has a 12 core biopsy obtained because a PSA reading is 6 and a small fraction (<10%) of one core has low grade cancer, the odds are overwhelming that the cancer will not impact on the patient's health or be a cause of death. The chart (Figure 1) is a valuable and powerful graphic demonstrating the likelihood of death from prostate cancer by age and by Gleason score from a large study of more than 700 patients for whom

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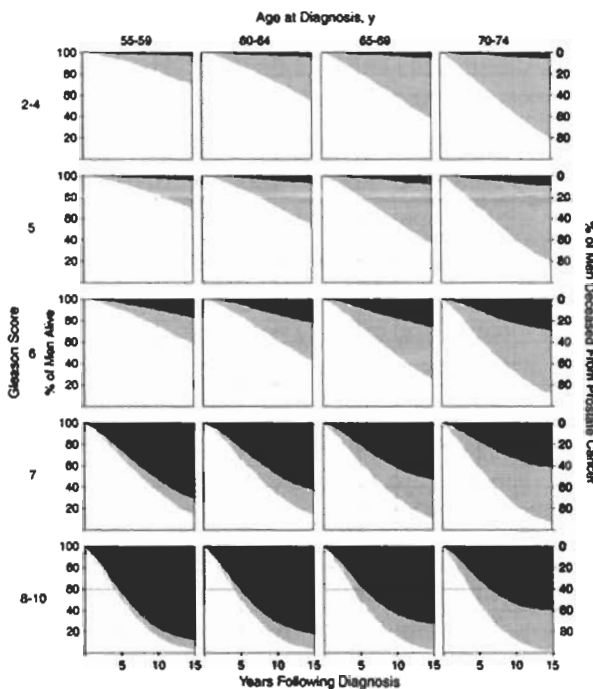


Figure 1. Survival (white lower band) and cumulative mortality from prostate cancer (dark gray upper band) and other causes (light gray middle band) up to 15 years after diagnosis stratified by age at diagnosis and Gleason score. Percentage of men alive can be read from the left-hand scale, and percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale. (From Albertsen PC, Hanley, JA, Gleason DF, Barry, MJ: Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA. 1998, 280:975-980).

RESEARCH UPDATE: Searching for prostate cancer signature proteins

By George L. Wright, Jr., Ph.D.

Virginia Prostate Center scientists recently published three sentinel papers in prestigious scientific journals describing the discovery of individual proteins and patterns of proteins that could potentially improve the early detection and diagnosis of prostate cancer. The first, entitled "Serum protein fingerprinting coupled with a pattern-matching algorithm distinguishes prostate cancer from benign prostate hyperplasia and healthy men," was published in *Cancer Research*. This paper describes the development and application of the SELDI ProteinChip[®] mass spectrometry protein profiling system as a potential diagnostic test for prostate cancer. The concept and development of this innovative assay was pioneered by the VPC scientists. Nine proteins were identified by this assay that produced a specificity of 97 percent in correctly differentiating prostate cancer from patients with benign prostate disease (BPH) and healthy men. It was also encouraging that organ confined cancer could be differentiated from non-organ confined cancer (i.e., cancer beyond the prostate gland) with a specificity of 87 percent. This suggests that certain protein alterations, once characterized, may be used to identify and differentiate patients with indolent cancer from those with the aggressive phenotype (*see previous article*).

Critical to the successful development of the SELDI protein profiling assay is the development and application of artificial intelligence computer algorithms for analysis of the tens of thousands of bits of SELDI mass spectrometry data. The development and application of these algorithms are being done in collaboration with scien-

tists at the Fred Hutchinson Cancer Center in Seattle, Washington. The pattern matching algorithm used in the study published in *Cancer Research* was able to discriminate BPH from prostate cancer with an accuracy of 83%. Although this differential diagnosis is better than can be achieved by the PSA test, further studies were undertaken to determine if this diagnostic accuracy could be improved because assays for early detection of cancer need to be highly accurate to avoid predicting too many false positives. A second algorithm applied to the same data set used for the *Cancer Research* study achieved an accuracy of 97 % in discriminating prostate cancer from BPH and healthy men. This later study was published in *Clinical Chemistry*. These two studies provide definitive proof-of-concept that the SELDI protein profiling system coupled with an artificial intelligence pattern matching algorithm provides an innovative and exciting new diagnostic tool for prostate cancer. Validation studies, using larger and more diverse sample populations and multiple SELDI instruments, are in progress at EVMS and other institutions to verify the clinical diagnostic utility of the SELDI protein profiling assay. VPC scientists are also obtaining similar results with other cancers, including bladder cancer, breast cancer, head and neck cancer, and leukemia. Details of these studies will be presented in future issues of the Newsletter.

The third study, published in *Clinical Cancer Research*, describes the discovery of potentially novel peptides (small proteins) by SELDI that may represent the early signals of a developing prostate cancer lesion. For

this study, pure populations of individual normal, benign (BPH), preneoplastic, and prostate cancer cells were obtained using a laser capture microdissection microscope. This specially designed microscope makes it possible to obtain pure populations of each cell type. This is extremely important to prevent contamination, i.e. mixture of cell types, so that accurate analyses can be performed. SELDI analysis of liquid extracts of the cells revealed several small peptides associated with either prostate cancer or BPH, with two peptides found in the preneoplastic (i.e., prostate intraepithelial neoplasia or PIN) and prostate cancer cells. These later peptides may be early protein alterations (i.e., signatures) of a developing cancer. If this proves to be true, it would provide concrete evidence that PIN is the early beginnings of a developing cancer lesion. Studies are in progress in the Proteomics Laboratory to isolate, purify, identify and characterize these peptides, and then to determine if they can also be found in body fluids (i.e. serum, urine, ejaculate) as diagnostic biomarkers. Once isolated and identified, studies can also be conducted to determine if these peptides are clinically useful targets for developing novel treatment strategies.

Overall, these three pilot studies illustrate the potential of the SELDI ProteinChip[®] mass spectrometry system for both biomarker discovery and as an innovative cancer diagnostic test. We are very excited and encouraged by these initial results and look forward to reporting the results of the validation studies. ■

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no active therapy was instituted and who were followed for more than 15 years through the Connecticut tumor registry. Patients who did manifest evidence of prostate cancer were treated with hormonal therapy but surgery and radiation were not employed. Using this chart, it is clear that young men with high grade cancer require surgery or radiation, or a combination of both, to avoid the likelihood of a prostate cancer death. However, elderly men with low grade cancer, in the absence of any surgery or radiation, have only a small percentage likelihood of prostate cancer death. Other causes of death far outweigh that of prostate cancer. A concise and sobering statement to illustrate these weighty considerations has been articulated: Death is inevitable but from prostate cancer only occasionally.

In the final analysis, it is the patient's decision concerning his diagnosis and his treatment that is followed. The physician provides data so that an appropriate informed decision can be made, taking into consideration the risks and benefits. The physician guides, the patient decides. Again it is critical that the patient's decision be based on useful and accurate information.

Finally, the "Holy Grail" of physicians, more than issues of the diagnosis and treatment of prostate cancer, is the identification of cancer with future lethal potential. To address this issue, analysis of body fluids, whether serum, urine, or ejaculate that can more accurately identify the existence and character of prostate cancer has been the object of investigation in the laboratories of The Virginia Prostate Center of Eastern Virginia Medical School and The Sentara Cancer Institute over the past decade as well as many of the laboratories in the country. Before this giant step can be realized the study of signa-

ture profiles in prostatic cancer tissue is a critical step. When these profiles are identified, they can then be analyzed in body fluids. Even the identification of the signature profiles, characteristics of aggressive cancer in tissue, as a preliminary step will be a great benefit. Men

difference between the pre-PSA era and PSA era baseline is significant. While undoubtedly there are patients in this group whose death will be prevented by the treatment of prostate cancer, there are a larger number of patients for whom the diagnosis is being made and

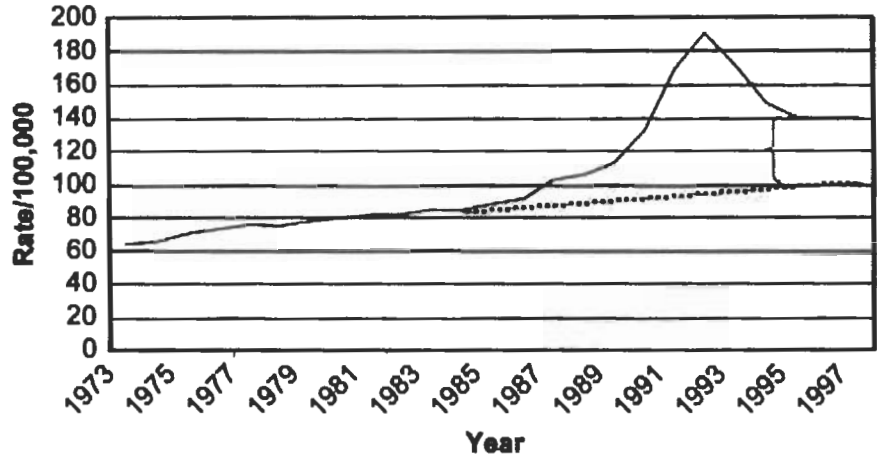


Figure 2. Surveillance, Epidemiology, and End Results Program age-adjusted prostate cancer incidence. Dotted line representing the pre-PSA era to facilitate a comparison with the new prostate cancer incidence at a steady state following the PSA peak. Difference noted by the bracket suggests an increase in the over diagnosis of prostate cancer. (From R.A. Stephenson, *Urol Clin N Am* 29 (2002) 173-181).

who have had a biopsy and the diagnosis of prostate cancer will have information about the potential of that cancer to behave in an indolent fashion and, therefore, no immediate therapy necessary, or aggressive, and therefore prompt therapy advisable.

The above effort addresses prostate cancer as the extraordinarily variable and heterogeneous malignancy it is and the need to tailor treatment rather than apply it universally or indiscriminately. As an illustration of the dilemma the chart (Figure 2) indicates the numbers that are currently available. The introduction of the PSA era, as would be expected, brought to the surface a number of cases of prostate cancer that would not have been diagnosed without the suspicion raised by the elevated PSA, which prompts biopsy and histologic examination for cancer. However, after a period of time, this "cull" effect should result in uncovering those unsuspected cancers and a return of cancer incidence to the previous baseline. The

treatment applied, who would never die from the disease within their allotted life span. This dilemma is well summarized by the statement that "in order to save lives from prostate cancer some patients will need to be treated unnecessarily." The aim of our current research is not only to reduce prostate cancer deaths by identifying those tumors with aggressive profiles that require prompt aggressive therapy, but also to identify those patients with prostate cancer who, because their disease is indolent, are very unlikely to reap any benefits from therapy. ■

Volunteers Needed

Men age 40 and older who have a diagnosis of prostate disease (prostatitis, benign prostate hyperplasia or prostate cancer), and men who do not have prostate disease are needed to donate body fluids for the SELDI Biomarker study. A compensation for the donation will be provided.

Those interested should call 757-446-7910.