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In this issue we continue William Ware's excellent series of articles dealing with the prostate and its problems. This month we cover the PSA test and the ongoing controversy regarding its appropriateness for screening purposes and the interpretation of its results. The decision to have or not to have the test is increasingly being left up to the individual patient, so it is extremely important to have as much information as possible available to aid in this decision.

My own personal feeling is that it can do little harm to have the test PROVIDED you do not act precipitously if confronted with a bad (positive) result. Most treatable prostate cancers grow very slowly, so there is ample time to repeat the test, undergo more refined forms of the test, make certain that prostatitis or BPH is not responsible for the PSA increase, and obtain a second opinion before agreeing to one or more biopsies and possibly subsequent treatments that can materially affect your quality of life. Personally, being over the age of 65 years, I would not proceed with a biopsy unless my PSA reading exceeded 10 ng/mL on two consecutive readings taken 3 weeks apart.

Also in this issue we report that potassium supplementation helps prevent bone loss; sun exposure may help protect against lymphoma; gum disease increases mortality among diabetics; and eradicating Helicobacter pylori helps prevent stomach cancer.

I continue to make additions to my web vitamin "store", so there are lots of new products for you to consider and, as a subscriber to our newsletter, you receive a 12% discount on already bargain prices. You can find the "store" at http://www.yourhealthbase.com/vitamins.htm. Please keep in mind that when you order, it is very important to begin the ordering process from this web page every time you place an order, rather than directly from the iHerb site. This way you will be sure to get your proper discount and I will be sure to get my commission.

Wishing you good health,
Hans

October Highlights

Potassium bicarbonate helps prevent bone loss

SAN FRANCISCO, CALIFORNIA. The type of diet, which most humans consume today, is very different to that of our ancestors. One difference concerns our shift away from potassium alkali salts, present in plant foods, and towards a greater intake of table salt and animal protein. This produces a net increase in the body's acid levels, which may contribute to the decrease in bone and muscle mass that occurs with age.

Postmenopausal women are at particular risk of age-related loss of bone mass due to calcium loss from bones. Studies suggest that treatment with oral potassium bicarbonate (KBC) can protect against bone loss by neutralizing the body's acid level. It improves the calcium and phosphorus balance and increases the rate of bone formation. The effects on calcium loss are measured through daily urine calcium excretion (UCaV).

Researchers from University of California tested whether the benefits of KBC are sustained over a longer time period in postmenopausal women. They followed 170 women for up to three years. Participants took either placebo or KBC at 30, 60, or 90 mmol a day, and all took a multivitamin including 400 IU of vitamin D. They were given additional calcium carbonate as required to provide a calcium intake of at least 30 mmol a day (1200 mg). NOTE: 30 mmol/day of KBC = 1200 mg/day of elemental potassium. KBC was effective at reducing calcium excretion in the urine. The effect increased with each increase in dose, and was maintained for the duration of the study. The twenty-eight per cent of women who had the highest initial UCaV showed the greatest effects.

The researchers calculate that women with high UCaV could accumulate the equivalent of nearly five per cent of their bone calcium content if treated with 60 mmol a day of KBC for three years. They conclude that it is possible to predict which women would benefit most, and the extent of the benefit of taking daily KBC. Previously, the same research team found that plant food intake is protective against hip fracture, and that hip fracture incidence correlates inversely with the ratio of plant-to-animal food intake.

Frassetto, L., Morris R.C. Jr, Sebastian, A. Long-term persistence of the urine calcium-lowering effect of potassium bicarbonate in postmenopausal women. ***Journal of Clinical Endocrinology & Metabolism****, Vol. 90, February 2005, pp. 831-4*

Sun exposure and lymphoma

STOCKHOLM, SWEDEN. It has been suggested that ultraviolet (UV) radiation exposure may be partly responsible for the increasing rate of malignant lymphoma. Certain studies have provided supporting evidence of an association, but it is still far from clear.

Researchers from the Karolinska Institutet set out to investigate the link. They conducted a population-based, case-control study in Denmark and Sweden, taking detailed information on history of sun exposure and other risk factors for lymphoma from 3,740 lymphoma patients and a similar number of healthy people. The patients' conditions included non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Hodgkin's lymphoma. Results showed that exposure to UV radiation were related to non-Hodgkin's lymphoma, but not in the direction that was expected. It appeared to decrease, rather than increase, the risk. The authors describe the association as consistent and statistically significant.

High ratings on various measures of UV light exposure such as sunbathing, sunburn and holidays abroad by the age of 20 reduced non-Hodgkin's lymphoma risk by 30-40 per cent. Moreover, risk dropped as exposure level increased. Increased UV exposure was linked less strongly to a decreased risk of Hodgkin's lymphoma. Previous skin cancer increased the risk of malignant lymphoma, as expected from earlier studies, so the researchers suggest that the link between skin cancer and malignant lymphoma is probably not due to UV exposure. They add that further evidence is needed before we can be certain that UV exposure is protective against lymphomas. Knowledge of the mechanism behind the effect is also necessary.

In an editorial accompanying the study, experts from the International Epidemiology Institute write that vitamin D may be a central mediator in the relationship between UV exposure and cancer.

They support the call for further research, given the major potential consequences for public health.

Ekstrom Smedby, K. et al. Ultraviolet radiation exposure and risk of malignant lymphomas. ***Journal of the National Cancer Institute****, Vol. 97, February 2005, pp. 199-209*

Egan, K.M., Sosman, J.A. and Blot, W.J. Sunlight and reduced risk of cancer: Is the real story vitamin D? ***Journal of the National Cancer Institute****, Vol. 97, February 2005, pp. 161-163*

Sun exposure: Both harmful and beneficial

ALBUQUERQUE, NEW MEXICO. UV radiation is a major risk factor for melanoma, a potentially deadly form of skin cancer. Rates of melanoma have increased over the past half-century, as has mortality from the disease, although they have risen less rapidly. Despite the confirmed causal link with sun exposure, recent studies suggest that UV radiation may also have a beneficial effect on melanoma survival. This is because areas with higher melanoma rates also have higher survival rates.

Researchers from the University of New Mexico investigated the possibility that increasing sun exposure increases melanoma survival as well as occurrence. They carried out a population-based study of 528 patients from the Connecticut Tumor Registry who had been diagnosed with melanoma in the late 1980s. Information was taken on sun exposure and history of skin awareness, suggesting early detection, and the participants were followed for five years. Increased levels of sun exposure - sunburn, high intermittent sun exposure, and solar elastosis (an indicator of sun damage) - and skin awareness were significantly linked to increased survival. Patients with solar elastosis had half the risk of death from melanoma as those without. Overall, the results could mean that sun exposure is protective or alternatively that early detection of melanoma is protective.

As found previously, further analysis showed that solar elastosis was independently linked to increased survival, so the authors conclude that sun exposure is indeed protective against death from melanoma. They suggest that the effect could be due to vitamin D production, or that sun exposure leads to less aggressive melanomas by increasing DNA repair functions which might reduce further mutational changes in the tumor.

Writing in an accompanying editorial, researchers from the International Epidemiology Institute encourage further work on the role of vitamin D in this area. They report that solar radiation is responsible for more cancers worldwide than any other single agent, but the idea that it may also be beneficial has long been considered. Commenting on the present study, they question whether the patients would have continued to spend time in the sun following diagnosis, so the results may not reflect continued sunlight exposure. The risks and benefits of sun exposure have to be weighed against many individual factors, they conclude.

Berwick, M. et al. Sun exposure and mortality from melanoma. ***Journal of the National Cancer Institute****, Vol. 97, February 2005, pp. 195-199*

Egan, K.M., Sosman, J.A. and Blot, W.J. Sunlight and reduced risk of cancer: Is the real story vitamin D? ***Journal of the National Cancer Institute****, Vol. 97, February 2005, pp. 161-163*

Meditation prolongs life

FAIRFIELD, IOWA. High blood pressure (hypertension) is a known risk factor for cardiovascular disease (CVD) and increases all-cause mortality. There is growing evidence that psychosocial stress is associated with high blood pressure and that techniques used to reduce stress may reduce blood pressure as well.

Researchers from the Institute for Natural Medicine and Prevention recently completed an analysis of two studies aimed at comparing transcendental meditation (TM) and other established relaxation techniques in their ability to reduce blood pressure, CVD and all-cause mortality. The studies included 77 white men and women (mean age of 81 years) and 125 African-American men and women (mean age of 66 years). The average baseline systolic blood pressure in the groups was 144 mm Hg. Study participants were randomized to participate in a usual-care control group or one of three relaxation groups. The participants were followed for an average of 7.6 years (maximum 18.8 years).

Early results indicated that TM lowered systolic blood pressure by about 10-11 mm Hg. Long-term follow-up showed that TM practitioners had a 23% lower incidence of death from all causes, a 30% lower incidence of death from CVD, and a 49% decrease in death from cancer.

The team concludes that the results show this 'mind-body' technique actually prolongs life, rather than simply reducing risk factors. They hypothesize that TM, or a similar stress-reducing method, may help lower mortality risk among those with high blood pressure. Earlier research on a possible mechanism suggests that the benefits could arise through normalization of the nervous system and hormones, which may have been distorted by chronic stress. The authors encourage further reliable trials in this area, especially focusing on minority populations, for whom data is lacking. They are currently running studies on other forms of complementary and alternative medicine with support from the US National Institutes of Health.

Schneider, R.H. et al. Long-term effects of stress reduction on mortality in persons ≥55 years of age with systemic hypertension. ***American Journal of Cardiology****, Vol. 95, May 2005, pp. 1060-1064*

Periodontal disease linked to mortality in type 2 diabetes

PHOENIX, ARIZONA. Previous studies suggest that periodontal disease - inflammation of the gums and bones surrounding the teeth - may contribute to the risk of heart disease. Periodontal disease occurs in higher rates among people with type 2 diabetes, possibly due to hyperglycemia, so it has been proposed that it may contribute to the increased mortality risk from diabetes.

Experts from the National Institute of Diabetes and Digestive and Kidney Disease looked into the effect of periodontal disease on mortality among Pima Indians with type 2 diabetes. They recruited 628 participants at least 35 years of age and followed them for about 11 years. Periodontal disease was recorded on radiographs and by clinical examinations. Among those with no or mild periodontal disease the adjusted number of deaths per 1,000 person years was 3.7. The equivalent number was 19.6 with moderate disease, and 28.4 with severe disease.

Specifically, periodontal disease was linked to heart disease and diabetic nephropathy (kidney disease due to diabetes). The authors report that, having taken into account a wide range of risk factors, severe periodontal disease was linked to 3.2 times the risk of these two diseases compared with people showing normal oral health. They propose that the teeth may be "a window into the heart", reflecting different aspects of the same inflammatory process. They suggest that periodontal bacteria might enter blood vessel walls and trigger hardening of the arteries. The link could also involve inflammatory markers such as C-reactive protein or fibrinogen - both risk factors for heart disease.

Other studies on periodontal disease have also indicated that it is associated with heart disease, heart attack and stroke. A recent report from Belgium found that 91 per cent of heart disease patients have moderate to severe periodontal disease, compared with 66 per cent of non-cardiac patients. It is not yet known whether treating periodontal disease can reduce the death rate from diabetes or heart disease.

Saremi, A. et al. Periodontal disease and mortality in type 2 diabetes. ***Diabetes Care****, Vol. 28, January 2005, pp. 27-32*

Eradicating H. pylori helps prevent stomach cancer

FUKUYAMA, JAPAN. Helicobacter pylori infection has been shown to be associated with stomach cancer risk in population-based studies. In animal studies, when stomach cancer was induced, H. pylori eradication therapy limited the spread of the cancer. Therefore, its eradication may reduce the risk of stomach cancer in susceptible humans.

Researchers from the Nippon Kokan Fukuyama hospital tested this hypothesis among people with peptic ulcer disease but no signs of stomach cancer. They recruited 1,120 patients, mostly men, with an average age of 50 years. The patients had either gastric ulcers, duodenal ulcers, or both and were treated for H. pylori infection. Treatment included the antibiotic amoxicillin and a proton pump inhibitor (to treat the ulcers). The patients

were tested for H. pylori status by endoscopy and a urea breath test one to two months later, and then yearly. Eighty-four per cent were cured of the infection.

Through following them for about three years, the researchers found that the likelihood of developing stomach cancer was lower among those who were cured of H. pylori. Compared with patients who were successfully treated, those with persistent infection had over three times the rate of stomach cancer. In the resistant group, four patients (2.3 per cent) developed the disease compared with eight patients (0.8 per cent) in the successfully treated group. All 12 cases of cancer occurred in those with gastric ulcer as opposed to duodenal ulcer. The authors conclude that eliminating the infection did not prevent stomach cancer completely, but point out that some of the cancers in the study may have been present but not identified at the start of the study. They write that persistent H. pylori infection is "an important international public-health issue", as it constitutes a significant stomach cancer risk factor. They believe that stomach cancer would be reduced in gastric ulcer patients if their H. pylori infection was eradicated with antibiotics, but call for larger-scale studies.

Take, S. et al. The effect of eradicating in patients with peptic ulcer disease. ***The American Journal of Gastroenterology****, Vol. 100, May 2005, pp. 1037-42*

RESEARCH REPORT

Diagnosis and Staging of Prostate Cancer

Part I – The PSA and DRE Tests

William R. Ware, Ph.D., Emeritus Professor of Chemistry, University of Western Ontario

INTRODUCTION

Before the blood test for prostate specific antigen (PSA) came into general use as a diagnostic tool for prostate cancer (PC), only abnormalities felt during a digital rectal exam (DRE) or symptoms suggestive of invasive cancer or metastasis such as bleeding or bone pain were available as indicators of the presence of this disease. The result was that many patients presented with non-localized or metastatic cancer, which in many cases was treatable only with symptom relief (palliation). In the late 1980s physicians using the new PSA blood test began detecting PC at a much earlier stage and a PSA cut-off was established above which a biopsy was indicated. Also, biopsy techniques improved and a grading system was developed for the analysis of tissue samples taken at biopsy which permitted the approximate differentiation between low-grade and perhaps biologically insignificant tumors on the one hand and potentially aggressive cancer on the other.

At present the PSA test is frequently done periodically in conjunction with physical exams and the majority of cancers now being detected are localized and viewed as curable by the surgical removal of the prostate (radical prostatectomy) or by radiation therapy. Prognosis in general is also now more accurately established, both preoperatively and after the pathological examination of removed prostates. PSA has also become a valuable tool in detecting recurrence (also called *biochemical failure*) after a radical prostatectomy or radiation therapy. It is also not uncommon to find evidence of PC in tissue removed during the transurethral resection operation (TURP) for benign prostatic hyperplasia, and even surgery for bladder cancer turns up unexpected PC. In spite of these advances, whether or not there has been an improvement in mortality for those with PC because of the use of the PSA test remains controversial and the subject of ongoing studies. This is an important question,

since surgical removal of the prostate (radical prostatectomy) or radiation treatment of PC are associated with adverse effects which can significantly and in some cases permanently decrease the patient's quality of life. As will be discussed below, this is not a simple matter and treatment decisions are far from straight forward.

When the PSA test is done on asymptomatic individuals, generally in the course of a physical examination, this is generally termed *screening*. Both the advisability of PSA screening and the appropriate PSA cut-off level suggesting a biopsy have become what are probably the most hotly debated subjects in the history of urology, and the large number of research results and associated editorials published annually continue to fuel the debate.

This review will examine the screening controversy, the utility and shortcomings of the DRE, the various aspects of the use of PSA in diagnosis and prognosis, the biopsy techniques in current use, the histological grading system known as the Gleason Score, tumor staging and the procedures used to determine if the cancer has spread beyond the gland. The goal is to provide detailed evidence-based information so that an individual can take part in the decision making process when options are presented. It is worth mentioning that the current trend is for these options to be discussed with patients since there are serious risk-benefit considerations involved which are far from clear-cut. For example, the current guidelines of the American Urology Association for the diagnosis of benign prostatic hyperplasia (BPH) [1] indicate that the PSA test should be *offered* to patients under certain circumstances. This highlights the problems associated with this test which include coping with the positive results that may occur, and implies a joint decision making process. In fact, on occasion one sees the principle stated that a diagnostic test should not be done unless it is clearly understood what action will be taken if the result is positive.

THE DIGITAL RECTAL EXAMINATION (DRE)

The male anatomy is such that the back of the prostate is in close proximity to the front wall of the rectum. This provides the opportunity for a physician to palpate (feel) part of the surface of the gland and estimate both the prostate size and the presence or absence of abnormal growths or other features. The area that can be palpated is where carcinoma most frequently begins. Carcinomas are characteristically hard, nodular and irregular. The test also has the potential for detecting extra-prostatic tumor. At the same time, the physician can check for abnormal rectal masses indicative of possible cancer. The procedure is essentially non-invasive but may be mildly uncomfortable or distasteful. In *Dr. Peter Scardino's Prostate Book* [2], the author points out that this test is highly subjective and difficult to master. Surface irregularities such as nodules may be strike one urologist as significant and another as insignificant.

The ability of the DRE to predict the presence of PC is not impressive. In a recent study of 408 consecutive patients with a mean age of 63.8 years and PSA ranging from 2.5 to 10 ng/mL, Philip *et al* [3] compared biopsy results with the observation of an abnormal DRE. Only 47% of the patients with an abnormal DRE had cancer on biopsy. There was also a poor correlation between the predicted stage and the actual pathology results for those that went on to have a radical prostatectomy. Also, a few patients with a normal DRE were found to have advanced cancer. The authors comment that in this study the examinations were done by two experienced urologists, and they suggest that that the accuracy might be even lower if the DREs were done by less experienced practitioners or specialist nurses.

Crawford *et al* [4] used a PSA cut-off of ≤ 4.0 ng/mL for normal and found in a large cohort that an abnormal DRE had a positive predictive value (percent of positives that were true positives) in the normal subgroup of only about 18% based on biopsy verified cancers, but for the group with an abnormal PSA and an abnormal DRE, the predictive value of the combined abnormal indication jumped to 56%, whereas for an abnormal PSA and a normal DRE, the percentage was about 28%.

It is common practice to do both a DRE and a PSA test in the course of a physical exam. The DRE can also provide information that is useful during the biopsy. Some urologists take extra samples (cores) in areas of the prostate where the DRE indicates potential tumors [2]. A recent study suggests that the DRE is underutilized [5].

THE PSA TEST

TOTAL PSA

PSA stands for prostate specific antigen. PSA is organ specific but not cancer specific. PSA is produced by cells in the prostate and released as part of the ejaculate. It was only in 1985 that the biological function of PSA was explained. After ejaculation, seminal fluid coagulates. PSA reverses this allowing sperm to achieve the required mobility. PSA is a macromolecule that cannot normally penetrate the prostate capsule nor find its way into the blood stream. Thus PSA should only be found in the prostate and in seminal fluid and under normal circumstances, only minute amounts are found in the blood. Thus measurable serum levels suggest that something has gone wrong in the structural integrity of the prostate. Candidates include prostatitis, benign prostatic hyperplasia (BPH), and PC. When the prostate is successfully removed, the serum PSA level is expected to drop to near zero and remain there. However, if metastasis has occurred or if some prostate tissue has been left behind, this can result in low levels of residual PSA that may progressively increase.

When used for diagnostic purposes, the PSA test is essentially a screening test. There are four possible outcomes, true positive, true negative, false positive and false negative. The validity of a screening test is frequently measured in terms of sensitivity and specificity. The former measures the ability of the test to correctly identify those with the disease, whereas specificity measures the success of the test in identifying subjects free of the disease. These two measures, given as percentages, are defined as follows:

- Sensitivity = true positives/(true positives + false negatives)
- Specificity = true negatives/(true negatives + false positives)

Too many false positives lead to poor specificity, whereas too many false negatives reduce the sensitivity. A specificity of say 50% would mean that there were as many false positives as true negatives.

The PSA test provides a continuous range of results and it is necessary to have a so-called cut-off value which defines positive (bad) and negative (good) results. Once this cut-off is agreed upon, studies which compare the test results to the actual correct diagnosis provide a measure of the value of the test. In the case of the PSA test, for example, a positive is by definition a value above the cut-off. When no cancer exists in the patient with a value above the cut-off, this provides a false positive. Likewise, when cancer is identified in a patient with a PSA below the cut-off value, the result is a false negative. Tests with less than perfect specificity and sensitivity simply provide probabilities of having or not having the disease in question rather than an absolute yes or no answer.

In the case of suspected prostate cancer, a biopsy is used to establish the diagnosis, although tissue collected during surgical treatment for BPH is also routinely examined for indications of cancer. An obvious and potentially serious situation arises when evaluating the merits of a screening test if the actual diagnostic procedure is not 100% accurate, which, as will be discussed below, is the case with prostate needle biopsies. An initial biopsy can miss as many as 30% of cancers, especially if it employs only six needles. Thus using one biopsy as an indicator of the presence or absence of cancer will make the PSA test, whatever the cut-off, appear less successful than it really is. Also there is interest in the relationship between the PSA serum level and the grade or aggressiveness of the cancer. The biopsy involves examining the cells in a set of cores obtained from the hollow needles used. For prostate cancer most pathologists use a system called the Gleason Score, which is based on the frequency of observing certain types of cells indicative of how advanced the cancer is. The Gleason score runs from 2 to 10, with a value of 7 or more indicating aggressive cancer. This will be discussed in detail below. Thus the pathologist examines the biopsy cores and makes several judgments, i.e. yes, no, or not clear that there is cancer present and if cancer is found, how much of what grade is observed. The yes or no answer can then be used in studies to judge sensitivity and specificity of the PSA test. The connection between tumor grade or score and PSA, however, is obscured by the fact that the grading is far from perfect, and when the biopsy results are compared with actual examination of the prostate, upgrading as well as downgrading of the score are far from uncommon, especially when the observations are made by pathologists who do not specialize in PC or see PC only occasionally. This will be discussed in detail when the biopsy is considered.

The cut-off of 4 ng/mL (*nanograms per milliliter is the only unit used for total PSA and therefore it will be omitted hereafter*) was established early in the use of the PSA test and was based on data collected in a private clinic setting. A serum level of less than 4 was considered insufficient evidence in the absence of an abnormal DRE for doing a biopsy, but this was purely a probability argument since it was well known that some patients in this "normal" group would in fact have positive biopsy results. The conventional wisdom dictated that many of the cancers found in this normal range presented no immediate danger. Many patients no doubt went away feeling good about their "normal" result.

Since the advent of the PSA test a number of studies have addressed the question of the prevalence of PC in patients having PSA ≤ 4; problems with this cut-off were brought to center stage in a landmark study by Thompson *et al* [6] published in the *New England Journal of Medicine* in May of 2004. The study participants (age 62 to 91) were drawn from the placebo arm of a drug intervention clinical trial, the goal of which was to determine if Proscar (finasteride), used to treat BPH, also prevented PC. In the placebo arm, 2950 men had both a normal DRE and a PSA level ≤ 4.0 over a seven-year period. At the end of this period, untreated patients who still met the criteria had a final PSA measurement and submitted to a biopsy involving a minimum of six needles. Thus the investigators were provided with tumor grading scores as well as PSA values for those in the cohort diagnosed with PC and those found free of cancer. Prostate cancer was diagnosed in 15.2% of the group and of those with PC, 14.9 % had a Gleason Score indicating advanced cancer.

The incidence of PC as a function of PSA is of particular interest. The prevalence was 6.6% for levels up to 0.5, 10.1% for levels between 0.6 and 1.0, 17% for levels of 1.1 to 2.0, 23.9% for levels between 2.1 and 3.0, and finally 26.9% for levels between 3.1 and 4.0. For those with a diagnosis of cancer, the prevalence of high-grade cancers increased from 12.5% for the PSA range up to 0.5 to 25% for those with PSA values in the range of 3.1 to 4. Two conclusions are evident: (a) the higher the PSA in this so-called normal range, the greater the probability of having prostate cancer, and the higher the PSA the greater the probability that the cancer it is high-grade; (b) there does not appear to be a threshold for PSA levels below which the probability of having prostate cancer is negligible. Even a PSA level of between the lower limit of detectability and 0.5 gave a one in ten chance of having PC and if one is unlucky, then in addition there was a 12.5% chance that this cancer would be aggressive.

The authors comment that their results run counter to the impression of many clinicians that PSA levels of 4.0 or less carry almost no risk of prostate cancer when in fact there is significant risk even of intermediate or high-grade cancer. In an editorial comment [7], Dr. Patrick Walsh of Johns Hopkins University Medical School, a very well know and respected urologist, remarked that if a patient really wanted to know if he had PC, the study of Thompson *et al* left one with no alternative but to suggest a biopsy, since measuring PSA clearly was not the answer. What he does not mention is that more than one biopsy might be necessary!

TO SCREEN OR NOT TO SCREEN

Do you want at PSA test? Should I have a PSA test? These are question that may come up in the course of a physical exam. The current trend in medicine is to provide the pros and cons of screening and encourage the patient to make the decision. This in fact reflects the current status of the screening debate. Thus the patient should be armed with as much information as possible, which is in fact a tall order given the complexity of the issues. Screening for prostate cancer involves a PSA test and/or a DRE in asymptomatic men. While it is common practice to do both, the debate on the merits of screening centers on the PSA test. A number of experts have advanced arguments for and against its use. While the debate goes back some time into the history of this test, it is of interest to review the arguments put forward in recent reviews and editorials [8-13]. These arguments are mostly based on the use of the test for total PSA rather than recent variations.

ARGUMENTS FOR SCREENING

- With the advent of widespread PSA screening in the US, the death rate from PC has declined, and in 1997 it fell below the rate recorded in 1986 when PSA was rarely measured. This is the mortality argument. Those on both sides of the argument appear mostly to agree that the cause and effect

relationship is still a hypothesis, and all await the results of ongoing trials. Preliminary results from one indicate no effect of screening on PC related mortality [14].

- Before PSA screening, many cancers were diagnosed at a stage that could not be cured. It is generally agreed that today most cancers are identified at a much earlier stage when the cancer is localized and can be treated effectively surgically or non-surgically. This is the "higher cure rate for tumors found early" argument. Treating early cancer was not in general possible before the PSA test because there simply was no way to find it. It was organ-confined and could not be detected with the DRE.
- As a screening test for PC, PSA has the highest predictive value. The only other screening test in routine use is the DRE.
- The majority of cancers detected with PSA screening are clinically important. Tumors that are large enough to elevate serum PSA are mostly not the insignificant, well-differentiated microscopic tumors found at autopsy in many, but not all men over the age of 50 who die from other causes.
- If one compares the incidence among cancer patients of palpable disease (positive DRE) for two periods 1983-1988 and 1999-2003, it was 92% in the pre PSA period and 17% in the recent PSA era, and the average PSA at diagnosis of PC dropped from 24 to 7.3.
- Incidence of positive lymph node and seminal vesicle disease (indicative of the spread of the cancer) is dramatically lower in the recent PSA era as compared to the earlier period. It is argued that this is due to early detection and equates to a better prognosis when the cancer is treated.
- Currently less than 10% of men have distant metastases at the time of diagnosis, which is considerably lower than was common in the pre-PSA era. Also, the percentage of men offered so-called local treatment with intent to cure (radical prostatectomy or radiation treatment) has increased significantly during the PSA era.
- The high false positive rate associated with either a 4.0 or lower cut-off can be decreased by adding %fPSA and PSA velocity (see below for a discussion of these two alternative PSA tests) to the screening protocol, thus minimizing biopsies that yield benign results, i.e. unnecessary biopsies.
- Advocates of PSA screening question the argument that screening leads to over-diagnosis. The study of Etzioni *et al* [15] found that the majority of cases of PC detected by screening in the population studied (60-84 years of age in 1988) would still have had cancer detected that presented clinically within the patient lifetime
- Some advocates of screening ask the following question. "Do those who are against PSA screening really want to return to the pre-PSA era when most of the cancers diagnosed were of an advanced stage and incurable?"

ARGUMENTS AGAINST SCREENING

- PSA screening leads to a large number of false positive results (PSA above the cut-off in cancer free individuals) which if acted upon, result in unnecessary biopsies.
- PSA screening finds insignificant cancers that would not yield clinical symptoms during the lifetime of the patient. Screening causes unwarranted treatment of slow-growing tumors. Advocates quote such figures as 14.5% of prostate cancers removed by radical prostatectomy are clinically insignificant, but the other side points out that this means that 85.5% of patients had clinically significant tumors that were removed, many of them successfully. This is reminiscent of the two points of view where a glass is termed half-full or half-empty.
- The decrease in mortality rate for prostate cancer seen during the PSA era is not due to screening but is the result of improved treatment including early hormone treatment and other still to be identified factors.
- A man's risk of death from prostate cancer is 3-4% whereas his lifetime risk of being diagnosed with the disease is about 17% [6]. This suggests that many prostate cancers detected in routine practice may be clinically unimportant.
- Unnecessary treatment results in unnecessary adverse effects such as impotence, incontinence and bowel disorders, and a decline in the quality of life of the treated individual. An increased risk of rectal cancer has also been recently reported associated with radiation treatment (RT) [16].
- The fear of dying from prostate cancer may be out of proportion with the real probability of death from this disease, given that approximately 250,000 US men were diagnosed with prostate cancer in 2004, but only 30,000 are expected to die from it [17].

Both the advocates and opponents of screening appear to agree that the relationship of PC specific mortality to the advent of screening remains to be settled, but there is no disagreement as to the occurrence of a mortality decline in a number of countries [18]. When PSA was first introduced in the late 1980s, both incidence and mortality increased, but this was followed after 1991 by an increasing decline. By 1997, the US PC mortality rates for white men aged < 85 had declined to levels lower than those observed in 1986. But there have been very few studies that addressed the question of cause and effect as regards the impact of screening on PC specific mortality. There is clearly a danger slipping into the logical fallacy *post hoc ergo propter hoc* (after which therefore because of)

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There appear to be only three studies that come close to properly addressing the question, and they are all recent. A study conducted in Quebec found a 62% reduction in mortality when screened and unscreened populations were compared [19]. This study came under immediate criticism for design and procedural problems [20] and another interpretation of the data yielded insignificant differences [18]. In another study [21], PC specific mortality in the Austrian state of Tyrol was compared to the rest of Austria. The motivation was that PSA screening was made more freely available in the Tyrol in 1993. While lower PC related mortality was observed in Tyrol as compared to the rest of Austria, another explanation for this difference may be the increased proportion of patients undergoing radical prostatectomies in this state, and in fact this predated PSA screening [22]. A third study was based on the fact that PSA screening was more common in the Seattle-Puget Sound area than in the state of Connecticut and this should have translated into a lower PC specific mortality. The results of this eleven-year study have just appeared [23] and were negative. Finally, PC mortality rates have also declined in countries where PSA screening is uncommon [24].

Confusing the issue even more is the just published case control study [25] that found the fascinating result that cholesterol lowering therapy employing the statin class of drug dramatically reduced the risk of prostate cancer (OR = 0.38, 95% confidence interval 0.21-0.69), especially more aggressive disease. A large prospective study is needed to examine this result since other studies, while not looking specifically at PC, did not find similar risk reduction. Needless to say, statin therapy is widespread and dramatically increased during the period when PSA screening was also increasing.

J.-E Damber has suggested [18] one explanation unrelated to PSA that could account for the decline in PC specific mortality. At about the same time as PSA screening became popular, there was renewed interest in hormonal therapy; its use increased substantially and it became common practice to begin this therapy earlier and even employ it in combination with radiation therapy. Damber reviews several randomized clinical trials of the use of the luteinizing hormone releasing hormone antagonist (e.g. goserelin) or castration along with radiation therapy which resulted in evidence of significant improvement in survival over radiation therapy alone. Even though hormonal therapy is not curative, Damber suggests that the increased use of this treatment could contribute to the observed recent decline in PC-specific mortality by delaying death from PC long enough for some patients to die from other causes.

The relevance of the mortality argument (screening is not advisable unless it has a positive effect on prostate specific mortality) should be scrutinized carefully. An individual can have metastatic PC that may go nearly to the end-stage, and yet die of a stroke or heart attack, and this would not be counted as PC specific mortality in some studies. Nevertheless, during the course of the disease, the individual would probably experience a greatly diminished quality of life associated with both the spreading cancer and its palliative treatment. The list of problems associated with advanced PC is long, but includes fatigue, depression, pain, numerous side effects associated with hormone and pain treatment, and problems once the cancer is established in other sites such as the brain, bone, lung, etc. A recent study was criticized for counting distant metastasis observed at autopsy as PC specific death, but the authors defended this protocol by pointing out that metastatic PC was in effect a death sentence. The point is that the effect of screening on the prevalence and time to onset of metastasis is perhaps a more realistic measure of its merits than looking simply at overall PC mortality. If early detection and treatment significantly delays metastasis in those not cured, the benefit would be is some cases dying of some other cause before metastasis profoundly altered the quality of life, a cause of death that would in some, perhaps even many cases be less drawn-out, debilitating, psychologically devastating and painful. There is recent evidence that screening and subsequent treatment have a significant influence on the incidence of metastatic PC [26].

A recent study carried out between 1991 and 2001 involving a very large number of participants directly relates to some of the questions raised in the screening debate and in particular the suggestion to lower the PSA cut-off for triggering a biopsy [27]. Included in the study were men 45-59 years of age at baseline with PSA ≤ 2.6 and a benign DRE who complied with a screening protocol involving periodic PSA measurements and a DRE. In this study, the indication for biopsy was PSA > 2.5 or a suspicious DRE. The six or greater needle biopsy procedure was used and not all men followed the recommendation for a biopsy. If one assumes that those refusing biopsy would have had the same cancer rate as those biopsied, then about 3% of those screened would have been found to have cancer. For those biopsied, 54% had cancer. Of these, 87% underwent a radical prostatectomy (RP), which yielded pathological characteristics of the tumor burden. Seventy-nine percent had organ confined disease, 13% possible harmless disease, and 2% possible rapidly progressing cancer.

Comparison via the published literature with non-screened populations provided the following observations, *all of which favored the screened population*: (a) 80% of the cancers were non-palpable, (b) no tumors were clinically advanced at diagnosis; (c) 13% of tumors were judged possibly harmless i.e. low over-diagnosis compared to non-screened populations. In addition, the five-year freedom from PSA progression (biochemical failure indicating eventual metastatic cancer) was 95% which is a very good recurrence free rate considering 10% had radiation treatment, 1.3% other therapy, and 1.7% observation only. Biochemical failure will be discussed below. The authors conclude that adherence to screening guidelines such as they employed would result in the detection of prostate cancer in most individuals that was both significant and curable.

One of the most persuasive arguments of the pro-screening advocates involves the assertion that finding PC early has a higher probability of leading to a so-called “cure.” If this is true then radical prostatectomy, which is frequently the treatment of choice, should be very effective in curing cancers identified by screening. While what constitutes a cure can be debated, one option is to consider the absence of an increase in PSA after treatment as an indicator of cure. If, on the other hand, the PSA level, after dropping initially to near zero starts increasing again (*biochemical failure*) then that would indicate that the cancer has not been eradicated.

Since 1992, at least twelve studies have addressed this question using biochemical failure as the endpoint [28,29]. While the populations studied had somewhat different characteristics, the five-year failure rate was found to be 2-20% and the 10-year rate 5-25%, Larger failure rates were associated with higher Gleason scores and higher preoperative PSA. Thus there appears to be some merit to this argument. The time lag between biochemical failure and clinical manifestation of disease may be as long as 5-8 years, followed by an additional 5-year median time to metastasis and another 5-year median time to prostate cancer specific death. Thus if biochemical failure occurs at, say, 5 years post-RP, then there would be on average about 15 years before PC related death would be predicted. But the problem of recurrence applies at most to only the 5-25% of individuals who had a RP. The remaining 75-95% were “cured.”

A study by Antenor *et al* [30] also addresses the above issue. They followed over 2800 men with the PC stage commonly found in screening studies who were treated with a RP and then monitored prospectively to obtain the 10-year biochemical progression free survival rates. Men with preoperative PSA in the range of 2.6 to 4.0 had an 88% 10-year disease free survival rate, i.e. a 12% failure rate, whereas for a preoperative PSA level > 10, the ten-year disease free rate was only 61%. Men with a PSA level of 2.6 to 4.0 also had the greatest rate of organ-confined disease, and the lowest Gleason score found post-RP. Similar results were obtained by Freedland *et al* [31] but the disease free survival rates were lower, even at 5 years. These studies viewed together support the notion of better prognosis with early detection, and as well suggest that a cut-off somewhere below 4.0 may have some merit.

Recent studies using PC-specific mortality as an endpoint provide a similar picture as regards to treatment and metastasis, but are based on comparing screening-initiated RP with a watchful waiting group where no treatment was given until palliation was required. This latter group is roughly equivalent to a pre-PSA or non-screened population. The largest difference between the RP and watchful waiting groups is seen with high-grade cancers [26,32]. One recent study with PC-specific mortality as the principal endpoint also looked at the effect of screening on subsequent distant metastasis and found the watchful waiting group at considerably greater risk than those randomized to RP [26]. Unless accidental death or a fatal comorbidity intervenes, patients with distant metastasis will die of PC.

While studies that favor screening continue to appear, it is clear that this debate will not be easily resolved until a new generation of markers and procedures with a much lower level of false positives and a better indication of tumor grade are devised, tested, and approved. The wide gap between the advocates (some call them evangelists) and those against screening (called snails who keep demanding more scientific proof) is clear from the fact that American Cancer Society, the American Medical Association, and the American Urology Association favor screening with PSA and a DRE, but the U.S. Preventive Services Task Force and the American College of Physicians recommend against it. This lack of agreement has resulted in a movement to shift the decision making burden to the patient. Frequently stated advice is that the physician should discuss the pros and cons of screening with the patient and obtain input as to whether or not to proceed.

There are two trials currently on-going in Europe that may help resolve the question of the relationship between screenings, the resultant early treatment, and overall PC specific mortality. Together these two trials aim to recruit over a quarter of a million men, but the results will not be available for several years. In a preliminary report from one of these studies [14], a favorable shift in prognostic factors was found in the screening arm of the trial, but the results failed to provide evidence that screening had an effect of PC specific mortality. In the meantime, the mortality argument should probably be viewed with suspicion.

AGE, SCREENING, AND THE AGE-ADJUSTED PSA CUT-OFF

The serum level of PSA is determined by both the presence of cancer and/or BPH, and as well can be elevated by other factors discussed below. BPH increases with age and thus provides a benign cause of age-dependent PSA elevation. But the matter is complicated because the probability of cancer also increases with age. A solution, proposed by Osterling *et al* [33] in 1993, involved an age-adjusted set of PSA cut-offs, with higher PSA levels associated with more advanced age. Subsequent studies showed that the use of these cut-offs reduced the biopsy rate in men with normal DRE, but Catalona *et al* [34] demonstrated that age-specific cut-offs missed large numbers of tumors. However, this approach to the use of PSA may offer greater sensitivity for cancer detection in younger men. An examination of the literature reveals that in the past few years there has been little interest in either improving or justifying age-adjusted cut-offs as a trigger for biopsy. There appears no solution to the fundamental characteristic of screening tests that, no matter what the age group, decreasing the cut-off increases the sensitivity of the test but reduces the specificity with the attendant increase in false positives [24,35].

Three high-profile books for the lay audience present age-adjusted cut-off tables [2,36,37], but aside from the work of Osterling *et al*, clinical studies justifying specific numbers as offering benefit to patients appear absent. If age-adjusted cut-offs, which have cut-offs below 4 for younger men, are use in practice the motivation is presumably detecting additional cancers, especially in younger men where there PSA elevations are more likely to be due to cancer since BPH is rarely a factor. The following guidelines for triggering a biopsy from Walsh's book [37] illustrate this. The first two thresholds are the same as proposed by Osterling *et al.*

AGE	PSA THRESHOLD
40-49	2.5
50-59	3.5
≥60	4.0

The most significant change from the traditional cut-off of 4.0 is in the 40-49 age group. There is considerable evidence that younger men with cancer, and in particular those below the age of 50 years, have a greater probability of organ-confined disease and a much higher disease free survival rate post RP [38-41]. In a very recent study [42] it was found that men younger than 62 with screening PSA < 4 had smaller, lower-grade tumors and lower recurrence rates post RP than those with PSA ≥ 4. This was not true for men over 62. A cut-off of 4 will fail to detect many of these small but highly treatable cancers. In fact, the Johns Hopkins urologist H. Balentine Carter [43] supports the lower cut-off of 2.5 for men under 50 whereas for all others he sees little advantage of lower cut-offs over the traditional value of 4, but this is the subject of debate, as will now be discussed briefly.

THE 2.5 VS 4.0 CUT-OFF DEBATE

Some of the arguments have been presented above. Facts that do not appear debatable include the following. The probability of detecting cancer is a direct function of the PSA level, and therefore the lower cut-off should increase the number of men above threshold who would presumably be counseled to undergo a biopsy, and this would result in finding cancers that otherwise would have escaped detection until the old cut-off was exceeded. A lower cut-off would also result in an increase in the number of benign biopsies, since lowering the cut-off has the inevitable consequence of decreasing the specificity of the screening test [24]. Another argument, as discussed above, is that lower cut-off will identify more younger men with PC, most of whom are curable.

Two papers by Catalona and associates [44,45] relate to the objection that a lower cut-off will detect too many insignificant tumors. They conclude that a cut-off of > 2.5 identifies a substantial number of cancers and will indeed find small, organ-confined tumors, but without over-detecting clinically insignificant cancers, but over-detection depends on how it is defined.

Carter [43] argues that there is no convincing evidence that with present-day therapy, men treated when their cancers are detected at PSA levels below 4 have any less favorable outcome than men treated when they exceed 4.0 by a small amount. But this argument is confounded by age, as Carter recognizes. He argues that the detection of PC at a younger age should have a greater effect on the probability of being disease-free after treatment than would the detection at a PSA of less than 4.

Like the screening debate itself, there appears no simple answer to the question of the optimum cut-off or the merits of using one lower than the traditional value of 4. The critical need is for new non-invasive tests that have both high sensitivity and higher specificity. Some of these will be discussed below.

FREE AND COMPLEXED PSA, PSA DENSITY AND PSA RATE OF CHANGE

The lack of specificity associated with the total PSA test (tPSA), has prompted considerable interest in refinements and variations that decrease false positives and false negatives. These “second generation” PSA tests include *free* PSA, *complexed* PSA, PSA *density* based either on total prostate volume or transition zone volume, and finally the rate of change of PSA with time expressed as a PSA *velocity* or *doubling time*. Complexed PSA appears to offer no advantage over the other second generation tests and will not be discussed [46]. Of special interest is improving the specificity in the 4-10 PSA range in order to reduce the number of unnecessary biopsies that a cut-off of 4 might provoke for individuals with total PSA levels in this gray area. But the PSA range of 2-4 is also of great interest, given that one in four men with PSA levels between 2.0 and 4 have PC at biopsy, more than a fifth of these lesions are judged high grade, and even a cut-off of 2.0 leaves 9% of men below this cut-off with cancer [6]. The need for greater specificity over the whole range from 2 to 10 is generally recognized.

FREE PSA

The form of PSA called free PSA is one of the most interesting in this context. While PSA is predominantly complexed with proteins, the form called free PSA (fPSA) is unbound. Early work suggested an enhanced discriminatory power of fPSA over total (tPSA), especially in differentiating PC from BPH. In fact, a crude generalization commonly seen is that bound PSA is from cancer cells and free PSA is from BPH (an enlarged prostate). This has prompted clinical trials of considerable interest. In these studies, free PSA is generally expressed as a percentage of total PSA, so:

%fPSA = 100 X fPSA/tPSA

A low value for %fPSA would thus tend to indicate the possibility of cancer while a high value would point toward BPH as the cause of the PSA elevation.

The %fPSA has been the subject of a number of studies aimed at evaluating its merits relative to tPSA for indicating the advisability of a biopsy [47]. The incidence of PC in the gray area of tPSA of 4-10 is typically 20-25%, but if everyone with a tPSA above 4 but below 10 is subjected to a biopsy, 75-80% will be benign. The

motivation in using %fPSA is to avoid some of these benign biopsies on the basis of a scheme that selects for those with low probability of PC. Thus the interest in determining if a suitable cut-off for %fPSA will accomplish this. The typical study is designed as follows. A group meeting a certain set of criteria (e.g. tPSA between 4 and 10 and a non-suspicious DRE) is recruited who are willing to undergo a biopsy. The %PSA is determined and from the biopsy results of the whole group, and merits of a given cut-off determined.

For example, in a recently reported large study [48], 500 patients underwent biopsy. In 107 PC was found, and thus 393 benign biopsies were generated by the tPSA cut-off of ≥ 4.0. If a cut-off for %fPSA of < 23% had been used instead as a biopsy trigger with this particular group, 77 participants were above this cut-off and would have avoided biopsy. Of the 77, 71 were actually benign and 6 had cancer. Thus the percentage of benign biopsies avoided by using this cut-off was 71/393 = 0.18 or 18%. The price for avoiding 77 biopsies was missing 6 cancers, all of which, according to the authors, were significant. The 6 cancers out of a total of 107 represents 5.6%, which allows one to judge the risk of avoiding the biopsy by making use of this %fPSA based cut-off rather than the >4 PSA cut-off. Since any cut-off can be examined from the data in hand, this type of study allows the selection of an optimum cut-off in the trade-off of avoiding unnecessary biopsies and missing cancers. If the desire is not to miss any cancers, then the exercise is pointless since it would be necessary to biopsy everybody. In this study, the overall incidence of PC was 107/500 or 21.4%. It is important that the incidence be comparable to that found in other cohorts since otherwise there would be a suspicion that the group did not represent the general public in the age range studied.

A second large study reported in 1997 [3] also dealt with the gray PSA area of 4-10 , but a high proportion of cancer cases was found (49%) which may not be representative of a normal patient population [48]. Nevertheless, when a 25% fPSA cut-off was used, 95% of cancers were detected while 20% of unnecessary biopsies were avoided. It is beyond the scope of this review to examine in detail the large number of studies related to the use of %fPSA, but it is frequently but not always found that a cut-off of 20 to 25% results is the avoidance of about 20% of unnecessary biopsies when the population studied has a total PSA in the range of 4-10. Since this gray area represents, for the majority of individuals, the PSA elevating effects of BPH, the use of the %fPSA for this range of tPSA involves an attempt to differentiate PC from BPH. Studies of %fPSA for men in the < 4 range are encouraging but limited [49], and it is too early to draw definite conclusions [49,50].

Along with the problem of the specificity of the PSA test, the other big challenge is to determine with some degree of certainty the presence of a significant tumor or tumors that indicates the advisability of aggressive treatment and at the same time exclude from either a biopsy or treatment those who have insignificant or indolent tumors that are judged to present little current risk and can be merely watched without putting the patient at undue risk. Evaluating a proposed protocol involves either the pathological examination of prostates removed at radical prostatectomy (RP) or an evaluation scheme based on a set of conditions applied to the biopsy core analysis. The information is combined with preoperative or pre-biopsy blood test data required by the proposed test. A number of studies have examined the %fPSA in this context.

In what Dr. Patrick Walsh describes [37] as a landmark study, Epstein *et al* [51] in 1998 reported the results of examining the power of %fPSA in predicting insignificant tumors in a series of radical prostatectomy cases. Insignificant cancers were defined as organ confined with tumor volumes of less than 0.5 mL and Gleason score of < 7. The best model for *preoperatively* predicting insignificant tumors was a %fPSA of ≥ 15% and favorable needle biopsy findings (less than 3 cores involved, none with greater than 50% tumor involvement). This model correctly predicted in the group studied that 17 out of 18 tumors were insignificant.

In a study based on radical prostatectomy samples, Southwick *et al* [52] examined a cohort with total PSA between 4 and 10 and a non-suspicious DRE. They also found that a cut-off of 15% fPSA provided the greatest discrimination in predicting a favorable pathological outcome. Aus *et al* [53] examined the use of %fPSA in predicting non-organ-confined PC, which would be classified as aggressive. For a %fPSA of 10.7% (first quartile), the risk of non-organ confined PC was 46.5%, whereas for the fourth quartile (> 20.7 %fPSA) the risk was 13.6%. Grossklaus *et al* [54] used tumor density (tumor volume divided by gland volume as determined in prostates removed during RP) as a measure of “tumor involvement” as estimated by either tPSA or %fPSA. It was found that the %fPSA correlated with tumor volume as well as Gleason score and extra capsular extension (tumor cells identified outside the prostate capsule). These results further support the notion that %fPSA is related to the aggressive nature of the cancer and that this has clinical significance.

A recent meta-analysis [47] systematically examined a large number of studies related to the use of %fPSA for men in both the 2-4 and 4-10 PSA ranges. The authors found that up to 50% of unnecessary biopsies could be avoided for those in the 4-10 range compared to 35% in the 2-4 range while missing 20% of cancers. From a somewhat different point of view, Dr. Peter Scardino [2] summarizes the results with %fPSA by pointing out that its use improves the ability by 20 to 40% to predict whether the cause of an elevated PSA is due to cancer but reduces by only about 5% the cancers that would otherwise not be detected. He also remarks that at one extreme, a %fPSA value over 25% suggests that elevated PSA is largely caused by BPH and any cancer present is more likely to be small and confined to the gland. A level %f PSA under 10% suggests that an elevated total PSA is mostly due to cancer and it is more likely than not that the cancer is significant and requires treatment. There is a gray zone between 10 and 25% where the picture is less clear.

Dr. Patrick Walsh in his 2002 book on prostate cancer [37] poses the question "Should you get it?" in reference to the %fPSA test. He introduces two points to consider. First, it is twice as expensive since two blood tests are required. This is an issue only if insurance does not cover the test or if it not on the approved list for public or private health care plans. The second consideration is simply the inevitable consequence of tests that are not 100% specific—5-10% of cancers may be missed. Walsh goes on to mention two situations where this test is, in his view, particularly useful. In the first case, there is the man with an elevated PSA who has had several biopsies that are negative. If the %fPSA is high, the patient can "relax." If the %fPSA is very low, this suggests that more biopsies are in order! The second situation involves an individual with a strong family history of PC but with a low age-adjusted tPSA. If the %fPSA is high, this provides reassurance that cancer is probably absent, whereas if it is low, it is an indication for a biopsy.

PSA DENSITY

The theoretical motivation for using PSA density (PSAD) is partly based on the fact that men with BPH will in general have both higher levels of PSA and enlarged prostates, and that this can be taken into account when trying to distinguish BPH from PC by dividing the tPSA by the measured prostate volume. Since BPH results almost exclusively from transition zone (TZ) hyperplasia, a refinement of the density argument introduced in 1994 leads to a density based on only the TZ volume (PSATZD).

Free and total PSA can be converted into densities by dividing by the prostate volume. The DRE is notoriously inaccurate in providing a measure of prostate volume, and thus the use of PSA density (PSAD) requires an ultrasound determination, generally with a transrectal probe. Since general practitioners and internists do not have such equipment in their offices, this necessitates a visit to the ultrasound facility at a hospital or diagnostic clinic. However, urologists may be able to provide these prostate density tests in the office setting. There is, incidentally, at least one study suggesting that trans-abdominal ultrasound is very much inferior to transrectal ultrasound in this context [55]. Total and TZ volumes can be obtained from ultrasound data available during an ultrasound guided biopsy, but this is irrelevant in the context of the problem of increasing the specificity of the PSA test if the purpose is avoiding unnecessary biopsies.

Most tests of the hypothesis that using a PSA density will improve specificity and avoid unnecessary biopsies involve comparing biopsy results with the levels of PSA density and some studies also include a comparison with %fPSA. The PSA ranges from 2-10 or 4-10 and ≤ 4.0 are of interest in this context. In a study by Horninger *et al* reported in 1998 [56], 308 individuals underwent ultrasound guided biopsy with 228 showing only BPH and 58 (19%) diagnosed with PC (22 had prostatitis). By using a cut-off of > 0.22 ng/mL/cc (the standard unit used) for the PSATZD as a biopsy trigger, 24.4% of negative biopsies could have been avoided. Djavan *et al* published a study [57] in 1998 that involved 559 consecutive men referred for early prostate detection or lower urinary tract symptoms who had tPSA in the range of 4-10 . The diagnosis of PC was based on one or more ultrasound guided biopsies. The PSATZD and the %fPSA were the most powerful and significant predictors of PC, and both were better than PSAD. By tolerating a 5% failure rate in PC detection, a cut-off of >0.25 ng/mL/cc as a biopsy criterion would have resulted in the lowest number of unnecessary biopsies. However, when the total prostate volume was less than 30 mL, the TZ based method was inferior to the %fPSA in sensitivity and specificity. Three much smaller studies published between 1999 and 2005 also examined the utility of PSATZD in diagnosing cancer while avoiding unnecessary biopsies. All involved participants with PSA in the range of 4-10. One study found PSATZD superior to PSAD [58]. Another found PSATZD superior to %fPSA [59] but the

third [60] failed to find an advantage over %fPSA. All three found a cut-off of 0.35 ng/mL/cc to give the best compromise between sensitivity and specificity.

Thus it appears that using a PSA density calculated from a measured TZ volume or combining this with %fPSA offers a protocol for decreasing the number of benign biopsy results for men with PSA levels in the gray area of 4-10 who would normally undergo biopsies simply due to exceeding the threshold of 4.0. However, the studies quoted would all have missed some cancers by using either the PSATZD or %fPSA or a combined indicator if their optimum cut-offs were used. By now it should be clear that this is inevitable.

There has been considerable discussion of the question of decreasing the "normal" cut-off from 4.0 to 2.0 or 2.5 for tPSA (see above). Thus tests that have improved specificity as compared to tPSA are of considerable interest for application to men with levels in this range. There have been several studies that address this question [55,61,62]. These studies examined the biopsy results for men with tPSA in the range of either 2.5-4.0 or 2.0-4.0 and relate to using the lower limit of these ranges as a cut-off that would trigger a biopsy. Djavan *et al* [62] studied 273 men with serum PSA between 2.5 and 4.0. The found that patients with a %fPSA > 41% and a PSATZD of less than 0.095 ng/mL/cc could safely been spared unnecessary biopsies. However, for small prostates (<30 mL), the PSATZD was less effective than in patients with larger prostates, and they suggest in this case the use of %fPSA alone. Koyayashi *et al* [55] found that PSAD and PSATZD were similar in terms of predicting PC in men with tPSA in the range of 2-4 and better than %fPSA.

In a small study, Ohi *et al* [61] found that the diagnostic efficiency of PSATZD showed the highest value for a cut-off of 0.23 and 0.28 for men with tPSA levels of 2.1-3.0 and 3.1-4.0 respectively, and that the use of these cut-offs as biopsy indicators would reduce unnecessary biopsies without missing most PC cases for men with tPSA in the range of 2.1 to 4.0.

The suggestion of lowering the cut-off for triggering biopsies from 4.0 to 2.0 or 2.5 mainly applies to younger men who are less likely to have BPH elevated PSA and who appear most likely to benefit from early detection and treatment of PC. For men who feel lower cut-offs are wise, have serum levels in excess of one or the other of these cut-offs and are referred to a urologist for consultation, a discussion of the possibility of using TZ based PSA density and %fPSA would seem to be in order when considering the pros and cons of a biopsy.

PSA VELOCITY AND DOUBLING TIME

PSA velocity (PSAV) involves repeated measurements over time to establish the pattern of change or stability in an individual's serum level. It has been known for a number of years that a rapid increase in PSA either in asymptomatic men or in those who have undergone treatment is generally a sign of trouble. As an adjunct to screening, PSA velocity is receiving ever-increasing attention. Some studies also calculate the doubling time. In the context of diagnosis a linear model is generally used, frequently with only two or three measurements. When PSAV is used in the post-treatment setting, it not uncommon to encounter a linear-logarithmic model used for calculating doubling times. Several recent studies are of interest.

Berger *et al* [63] recently reported on a large study where men were followed for up to 10 years (average 6 years). In this retrospective study 2,462 men without PC underwent PSA testing every two years. Over the total time period 353 patients were diagnosed with PC. In men with cancer mean tPSA increased from 2.28 at baseline 10 years before diagnosis to 6.37 at the time of positive biopsy (PSA velocity 0.409 ng/mL/year). In the benign group, the mean tPSA increased from 1.18 to 1.49 over ten years for a velocity of 0.03 ng/mL/year. For subjects with tPSA levels of 2 or less two years prior to diagnosis, 11.4% had values of more than 4 at the time of positive biopsy. The authors concluded that an annual measurement was not required for men with levels below 1.0, but for those above this level annual measurements were suggested on the basis of the observation that a significant percentage of men with initial levels > 1.0 had levels of over 4 two years later. Finally, an interesting observation was that about 24% of men with no evidence of PC had *lower* tPSA values at the end of the study than the value found 10 years earlier. They also comment that the currently used threshold velocity of ≥ 0.75 ng/mL/year may be too high, at least in a Caucasian population. However, two early studies, one in 1992 [64] and one in 1994 [65] found that a cut-off of 0.75 ng/mL/year was optimum for distinguishing men with high risk of progressing to PC or as a biopsy threshold. It was found that when the PSAV was based on a time span of 18 months or more, 95% of men without PC had a PSA less than 10 and a PSAV less than

0.75 ng/mL/year. Dr. Peter Scardino [2] also takes the position that a PSA velocity of more than 0.75ng/mL/year indicates an increased risk that a biopsy would be positive for PC.

In a small study published in 2002, Fang *et al* [66] studied men with initial PSA levels between 2.0 and 4.0. Men who maintained a PSAV of less than 0.1 ng/mL/year had a 97% probability of remaining disease free for at least 10 years compared to only 37% for those with a PSAV exceeding 0.1 ng/mL/year. Their data indicated that 80% of PC cases could be identified with this cut-off, but the false positive rate would be 50%.

Large annual increases in PSA prior to diagnosis are a strong indication of poor prognosis [67]. Two recent studies strongly suggest that a PSAV of greater than 2 ng/mL in the year preceding diagnosis predicted poor outcome following either RP or RT [68,69]. metastatic disease with progression following hormone therapy after RP.

There have been a few other studies that address the utility of PSAV, but they are difficult to compare due to different designs and populations studied [70-72]. As Dr. Patrick Walsh points out [37], PSAV offers an improvement over the raw PSA score but it is important to realize that 25% of men with prostate cancers that are growing do not have a big increase in their PSA. Like the other variations of the PSA test, perfection is not in sight. Nevertheless, PSAV appears to add a significant piece of information, not only if the PSAV is very low but especially if it is very high. The usefulness of PSAV also provides a rationale for annual or biannual testing in order to acquire the necessary data. Once a man has agreed to have a PSA test, it can be argued that it makes sense to continue the practice for this reason.

INTRA-INDIVIDUAL VARIATIONS IN MEASURED PSA

A serious problem associated with PSAV, as well as with PSA cut-offs in general, involves the intra-individual variations. In a recent study, Boddy *et al* [73] tested men with biopsy demonstrated absence of PC. Four measurements of PSA levels were made over one month. The average variation was almost 10%, and when stratified by PSA level, 0-4.0 gave, 14.1%, and 4.1-10 gave 10.8% variability. The authors review earlier studies which showed similar variations, with typical values of about 15%. A 15% variation takes a value of 3.9 to 4.5. Variations of this magnitude are of consequence when either PSAV is being tracked or a patient crosses or is near a cut-off. For example, Eastham *et al* [74] examined 972 men and acquired five consecutive blood samples over a 4-year period. Among men with an abnormal PSA result, a high proportion had a *normal* result at one or more subsequent visits during the follow-up period (44% with an initial PSA result > 4, 40% with an initial level higher than 2.5 and 55% with an initial elevated level above the age specific cut-off). The authors conclude that an elevated PSA (i.e. one that crosses a cut-off), should be confirmed with a repeat test several weeks later before attributing clinical significance to the result.

ARTIFICIAL LOWERING OR ELEVATION OF PSA

The following factors can raise or lower serum PSA levels to an extent that can be significant in connection with both cut-off crossing and PSA velocity measurements.

- The DRE can artificially raise PSA levels for a day or more. The largest immediate effect is on %fPSA. For example, in one study, the average value from before to 30 minutes after the DRE for total PSA was 3.4 to 4.3 and for %fPSA from 27.9 to 38%, with both changes highly statistically significant [75]. Thus blood for a PSA test should be drawn before a DRE.
- Both total and free PSA increase after ejaculation with different rates of return to baseline. PSA testing within 24 hours of ejaculation may lead to an artificial elevation and erroneous clinical conclusions [76].
- Bladder cystoscopy and/or catheterization can elevate PSA levels for at least two weeks.
- Laboratories using different assay procedures (kits from different companies) can produce variations that have significance when the value is near a cut-off or when PSA velocity is an issue. In a recent study of two currently used commercial assays, 19% of patients would have been candidates for a biopsy with one test but not with another used in comparison. The cut-off in this study was 4.0 [77]. This is a serious problem since changing primary care physicians is not uncommon, and physicians may change the laboratory they patronize.
- Acute urinary retention can elevate PSA levels for up two weeks.

- Prostate needle biopsy or TURP to treat BPH can elevate PSA values for up to six weeks.
- The two medications used to treat BPH, Proscar and Avodart; both reduce PSA levels by about 50%. Incidentally, Propecia used for treating hair loss is low-dose Proscar **(**finasteride). Some physicians correct for this but it is hard to believe that the correction is more than just approximate.
- Prostatitis can strongly elevate PSA levels, but they will generally come back down with antibiotic treatment.
- It has just been reported in a small study that statin treatment for hypercholesterolemia can lower PSA levels [78]. The study involved 15 airline pilots. Over about 6 years, the average PSA dropped 41.6 % in the statin group and increased by 38% in the comparison group, the latter increase presumably being age related. These are large and statistically significant changes. This will no doubt receive additional study in the next few years since the number of men taking statins is very large indeed and there is pressure to increase the number by lowering LDL cholesterol targets. The mechanism of the interaction is unclear as is the answer to the question, did this reduce the risk of PC? Thus while these results need confirmation, statins appear to significantly interfere with the use of PSA cut-offs for diagnostic purposes. Also, there is actually some evidence that statins do in fact decrease the risk of PC [25,79,80].
- While PSA on average increases with age, across age groups men with greater Body Mass Index (BMI, weight in kg divided by the square of the height in meters) have significantly lower total PSA. Obesity (generally BMI > 30) appears to affect the level of PSA mainly in the range of less than 4. This is relevant to the use of adjusted cut-offs and may also impact diagnostic accuracy [81]. Age *and* BMI adjusted tables have been suggested.

The information provided above should be of value to men prior to getting a PSA test and as well, men should be aware of alternative reasons aside from prostate cancer might explain an elevated PSA. Most physicians will of course consider these various factors, but men should be informed simply on general principles. Also, an artificially reduced value could mask the presence of cancer, and it is important that men inform urologists if they are taking statin drugs or 5-α-reductase inhibitors such as Proscar, Avodart or Propecia. The statin effect was reported only recently (2005), and many physicians, especially internists and GPs, may be unaware of it, especially if they do not religiously read the *Journal of Urology*!

CONCLUSION

There is no clear consensus within the medical community as to the advisability of having a PSA test. One side maintains that the test saves lives by precipitating early treatment while the other side maintains that the test is so inaccurate that it often leads to unnecessary biopsies and treatments that can seriously damage a man's quality of life. Ultimately, the individual must decide whether to have the test or not. This decision should clearly include a careful consideration of what exactly the individual is prepared to do in the way of follow-up investigations and treatment if the test indicates a problem.

In view of the fact that the vast majority of treatable prostate cancers grow very slowly there would seem to be no need to panic or make any rash decisions upon receiving a single bad result (high PSA value). A repeat test three weeks or so after the initial test would certainly seem prudent. If that is also positive (PSA value above cut-off point) then other tests such as free PSA, PSA density and, depending on the magnitude of the PSA value, PSA velocity should also be considered before submitting to a biopsy, which as we shall see in Part II of this report, is also associated with a whole raft of inadequacies and potential side effects.

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