SEATTLE PROSTATE INSTITUTE

# PCa Commentary

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## Contents


| | | Page |
|---|---|---|
| **PATHOLOGY** | **"Prostatic Intraepithelial Neoplasia (PIN) - When stuck with PIN what should be done?"** | **1** |
| **BASIC SCIENCE** | **Gene Expression Silencing in PIN Cancels the Detoxification Enzyme Glutathione** | **2** |
| **DIET & PREVENTION** | **Does Selenium Prevent Prostate Cancer? Someone is bound to ask you** | **3** |


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### PATHOLOGY

Prostatic intraepithelial neoplasia (PIN) presents a vexing problem for risk prediction and evidence based management. It also raises challenging issues relating to the genesis of prostate cancer. It has been much studied, but satisfactory answers to the questions it poses await a more complete understanding of its basic biology.

High grade PIN (HGPIN), the lesion of interest in this discussion, consists of an abnormally compact cluster of small glands in which the organization of the epithelial cells is irregular; the cells are not consistently uniform in size and have abnormal nuclear features; and the basal cell layers of the glands (acini) are often disrupted. HGPIN can be present in the prostate in a spectrum ranging from focal to extensive. The key issue is whether this lesion is an obligate precursor of prostate cancer - a sort of stage 1/2 -, or a worrisome marker for the likelihood of recognizable prostate cancer occurring simultaneously or subsequently. It's deemed quite possible that both processes result from some not yet clearly identified "field effect" predisposing a prostate to both cancer and PIN. Optimal management of a patient with HGPIN depends on resolving this issue. Uncertainty in this area impacts the practical question of when and whether to conduct follow-up prostate biopsies.

Two major areas of study have been: 1), understanding the relationship of PIN to cancer; and 2), what is the best re-biopsy strategy. Regarding the first issue I'll focus on work of Dr. Wael Sakr, who along

with Dr. Alan Partin, updated many years of work in the article "Histological Markers of Risk and the Role of HGPIN" (UROLOGY 57, Supplement 4A, April 2001. pp 115-120). They report the culmination of their very careful studies of prostate glands from autopsies of 652 men ( 20 to 80 years of age) who died from non-prostate cancer causes. The prevalence of HGPIN (in 211 caucasian men) from the third to eight decade was 8%, 23%, 29%, 49%, 53%, and 67% (in African American men the prevalence was higher). *Extensive* involvement (third - sixth decades) was 0%, 2%, 5% and 12%. PIN was found in 63% of men in whom prostate cancer was discovered and in 25% with no evidence of concomitant PC. Other autopsy studies report PIN in association with cancer in 63% to 94%, whereas in benign prostates HGPIN was present 25% to 43%. When Sakr classified HGPIN as extensive, intermediate, or focal, an association with cancer occurred in 76%, 51%, and 36% respectively. Clearly the work of Sakr and many others establish the frequent association of HGPIN with PC. However, whether this lesion is a true presursor of PC, i.e "premalignant", is still not known.

How should this information affect management of a patient "stuck with PIN"? For this discussion I'll refer to the work of Dr. Gary Lefkowitz, New York University Medical Center, who has very carefully addressed this issue over years and summarizes his work in "Follow-up Interval Prostate Biopsy 3 Years After Diagnosis of HGPIN Is Associated With High Likelihood Of Prostate Cancer, Independent Of Change In PSA Levels" (The JOURNAL OF UROLOGY,Vol 168, October 2002, pp 1415-1418). The important feature of his work is that all data is based on 12 core sampling. The study reviewed 1223 biopsies performed because of a suspicion of PC due to an abnormal PSA or DRE. 119 (9.7%) showed HGPIN. The 72 men who had initial 12 core biopsies showing HGPIN also had followup biopsies during the following year. The mean baseline PSA was 6.88 ng/mL. At the repeat biopsy cancer was found in 2.3%; 45% continued to show PIN, and 48% showed no disease. The mean PSA for all men at repeat biopsy was 9.7 ng/ml, an insignificant change. This study is unique in presenting 3 year followup data on the group that showed PIN on the study entry biopsy. At 3 years 25.8% showed PC, 35% PIN only, and 38.7% no disease. Lefkowitz noted as have others that HGPIN is frequently multifocal in distribution. Lefkowitz recommends re-biopsy at least by three years after an intitial diagnosis of HGPIN. He acknowledged that his data did not allow a recommendation for re-biopsy at an earlier time. The Lefkowitz study is at varience with other studies that show 30%, 44%, and as much as 50% PC at intervals usually up to one year after an initial finding of HGPIN. In this discussion I have, however, focused on Lefkowitz's work because of the thoroughness of analysis, consistency of pathological diagnosis, and the three year follow-up. Interestingly, one study from a Netherlands group (CANCER August 1, 2001 pp 524-534) reported finding HGPIN in .8% of 4057 men who had participated in a popoulation-based screening study in which biopsies were done for abnormal PSAs and DREs. When men with HGPIN were rebiopsied at one year cancer was found in 10% (3 of 30). Re-biopsy of men who had intitially shown no biospy abnormalities showed PC in ll% (51 of 452). They concluded that rate of PC development for men initially showing HGPIN was the same as the de-novo presentation of PC.

**Bottom Line**: After much study a good deal has been learned, but it would be helpful to be able to determine at the outset which HGPIN is going to be a troublemaker (other than those with an extensive and mutlifocal presentation). Possibly the discussion presented below will be a start in that direction.

## BASIC SCIENCE

The question of whether HGPIN can be identified as a precursor to PC was addressed by Dr. Sidransky, Professor of Urology and Director of Research in Molecular Biology at the Johns Hopkins' Kimmel Cancer Center in the article, "Quantification of GSTP1 [Glutathione S-Transferase] Methylation in Non-neoplastic Prostatic Tissue and Organ Confined Prostate Adenocarcinoma" (JNCI, November 2001). "Methylation" refers to the presence of a methyl group attached to a member of the

sequence of bases in the DNA chain (in this case, specifically, the base cytidine in the promoter region in the gene) thereby preventing the transcription mechanism from "reading" the gene and thereby "silencing" it. Methylation is one of nature's favored mechanisms for selecting which genes should and should not be expressed and when that expression should take place in the sequence of development. The polymerase chain reaction assay was employed to identify the obstructing presence of methylation preventing the expression of the GSTP1 gene thereby depriving the cell of the benefits of the detoxifying enzyme glutathione. Glutathione provides an important element of protection against oxidative damage to DNA, damage that can lead to DNA strand breaks and unwanted mutations. The methylation of this specific gene is the most common adverse alteration of DNA in prostate neoplasia and develops very early in the disease process. In his study of 69 prostatectomy specimens with organ-confined adenocarcinoma 63 showed this abnormality. Twenty eight of these specimens contained both PC and HGPIN, and in 15 of these HGPIN showed methylation of the GSTP1 promoter. In a separate study of TURP specimens 9 of 31 showed methylation. However, when the *extent* of methylation in PC, HGPIN, and BPH was evaluated quantitatively, significant separation of the results was found among the three types of lesions. These results were compared to a control lesion with no methylation to establish a ratio of expression, and the median ratio of methylation in BPH (from the TURP study) compared to control was 0 (range 0-0.1); in HGPIN 1.4 (range 0-49.5); and in PC 250.8 (range 53.5-697.5), raising the intriguing issue of whether the extent of GSTP1 methylation in HGPIN lesions predicts progression to invasive cancer. Since histologic identification of the suspected transition from HGPIN to PC has been elusive, perhaps by evaluating the levels of methylation in HGPIN lesions pathologists can establish persuasive evidence of this transition. Perhaps by quantitating methylation in HGPIN it would also be possible to place a specific instance of HGPIN at its appropriate position along the suspected spectrum of progression toward recognizable prostate cancer. Understanding of this sort would have an impact on the management of this vexing lesion. The GSTP1 test can be performed on paraffin-embeded tissue tissue from prostate biopsies and could be used in retrospective studies. This issue is under active study at Johns Hopkins.

**Bottom Line:** Additional data will be coming from Dr Sidransky on this important issue.

## DIET AND PREVENTION

Should all men take 200 mcg selenium to prevent prostate cancer? The answer is currently straightforward. No one knows. Otherwise it would be unethical to conduct the SELECT Trial (Selenium and Vitamin E Cancer Prevention Trial) which addresses this question by comparing the outcome of men taking selenium 200 mcg, or Vitamin E 400 mg, or a combination of the two or placebos. This study was commenced in July 2001 with a goal of recruiting 32,400 men. Dr. Gary Goodman at the Swedish Hospital Cancer Institute is the local coordinator and information about registration is available at 215-3245. Because of the long incubation period preceding the clinical detection of PC the trial is scheduled to run 12 years. Four other trials are also addressing intervention with selenium 200 mcg/day: one for men with high PSAs and negative biopsies; a three year SWOG study for men with HGPIN; a study to evaluate the cellular effects of selenium administered for 6 to 8 weeks before prostatectomy; and a "watchful waiting" study for older men with PC who choose to defer definitive treatment. Collectively, these studies will provide guidance for the future management, and men without established opinions on this issue should be encouraged to participate. However, many men will feel that "time is short and science is long" and choose to hedge their bets by taking the 200 mcg. There is a strong body of epidemiological and laboratory support for their choice.

Why selenium? Selenium is a non-metalic trace element found in alkaline soil which enters the food chain via wheat, corn, forage crops, and nuts. The current dietary recommendation is 20 - 40 mcg daily. This element and subsequent metabolic products are combined with amino acids, i.e.

selenomethionine, and incorporated into many enzymes. Selenomethionine is a necessary component of glutathione (mentioned above). Two early nutritional studies focused interest on selenium's role in cancer prevention. Yoshizawa (JNCI,Aug,1998)reported a "Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer". 33,737 men submitted clippings; 181 cases of PC were diagnosed during the study; and when compared to the lowest quintile values of selenium men in the highest quintile had 65% fewer cancers. The second study was first reported by Dr. Larry Clark in JAMA, Dec 1996 and updated July 2002. It was based on the 1312 man Nutritional Cancer Prevention Study conducted primarily to evaluated selenium's affect on skin cancer This study compared 200 mcg/day selenium to a placebo. It was noted that 28 men developed PC during the study: 13 who had taken selenium compared to 35 in the placebo group.

What basic cellular mechanisms might explain selenium's postulated role in PC prevention? Until recently selenium had been assigned two roles: as an antioxidant and an inducer of apoptosis. Prostate cells are persistently subjected to extensive risk of injury from the reactive oxygen free radicals resulting from the metabolism of androgens. And selenium serves as a major scavenger of these mutagenic agents. The glandwide risk resulting from this adverse environment may, in fact, be the "field effect" that underlies the very frequent multifocal distribution of PIN and PC in the prostate gland. As an inducer of apoptosis (programmed cell death) selenium contributes to the elimination of damaged, potentially cancerous cells. In a 1998 study Clark found in tissue culture that selenium caused greater growth inhibition to PC cells than normal cells.

The newest information on the cellular function of selenium comes from two recent articles in the JNCI. In the January 2003 issue selenomethionine is reported to initiate DNA repair, a process key to correcting adverse cancer causing mutations. The data suggests that selenium activates the p53 gene, a master regulatory enzyme that monitors quality control by promoting DNA repair or, alternatively, induces apotosis in hopelessly damaged cells. When activated, the gene turns on 100 or so other genes that effect repair or apoptosis. Selenium increases this activity threefold compared to control. There is a downside to this discovery, however, since this scenario requires that p53 gene is fully functional, i.e. non-mutated. Unfortunately, in possibly half of all cancers, p53 is non-functional due to mutational injury. However, in PC this inactivation of the p53 occurs late in the cancer process, allowing the hope that selenium, when used early as chemoprevention, will find a functional p53 to work with. The final article (JNCI, February 2003),"Effects of Dietary Selenium Supplementation on DNA Damage and Apoptosis in Canine Prostates", brings the investigations closer to man ("dogs and humans,[are] the only two species in which prostate cancer develops spontaneously with appreciable frequency"). The dogs were treated for seven months before their prostates were examined. The authors concluded: "dietary selenium supplementation decreases DNA damage and increases epithelial cell apoptosis within the aging canine prostate."

**Bottom Line**: What to do? Robert Frost alludes to our current situation: "We dance round in a ring and suppose, but the secret sits in the middle and knows." In time the clinical studies may reveal the secret.