It was in 1987 that McNeal and Bostwick\textsuperscript{1} first described intraductal dysplasia during a whole-mount pathologic investigation of 100 prostates without cancer and 100 with cancer that were diagnosed in the pre–prostate-specific antigen era. They found foci of dysplasia in 82\% of the prostates harboring cancer compared with 43\% in those without cancer. Interestingly, both the grade and volume of dysplasia were associated with cancer risk. With that report, pathologic evaluations of the prostate began to annotate the presence of prostatic intraepithelial neoplasia (PIN). Initially, the finding of PIN led to series examining the likelihood of finding cancer on rebiopsy after a finding of PIN (high risk) and then studies examining the molecular characteristics of PIN (found to be similar to cancer).

For perhaps two decades, it was generally thought that PIN (often called high-grade PIN) fulfilled the criterion for a premalignant lesion. If such were the case, it would more effectively identify a much smaller group of high-risk men to study for chemoprevention, compared with the general population used to evaluate finasteride in the Prostate Cancer Prevention Trial.\textsuperscript{2}

Two large-scale PIN-to-cancer chemoprevention trials then ensued. The first was a National Cancer Institute study of selenium (on the basis of extensive preclinical data) that recently reported negative results.\textsuperscript{3} This is not surprising, given the negative findings of the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a chemoprevention trial using selenium and vitamin E that found no change in risk with selenium but a 17\% increased risk of cancer with vitamin E.\textsuperscript{4} In the article by Taneja et al\textsuperscript{5} that accompanies this editorial, the second of these studies is described: a large, randomized study of toremifene, a selective estrogen receptor modulator, which in a previous smaller study had demonstrated promising risk reduction. Unfortunately, overall and in subsets, no effect of toremifene was noted. What was remarkable, however, was what seemed to be the high risk of cancer development in a relatively short period of time: 32.3\% of the men in the placebo group were diagnosed with cancer, and the 3-year cancer-free survival was 54.9\%. Examining the Kaplan-Meier figure might lead a reader to conclude that, ultimately, the majority of these men would be found to have cancer—a premalignant lesion, indeed!

The challenge with reaching this conclusion relates to the relatively high probability of a cancer diagnosis in a population of this age (median age, 65 years). If we use the Prostate Cancer Prevention Trial Risk Calculator to estimate the average risk of men in this study for a cancer diagnosis on a single repeat biopsy and assume that all risk factors other than the digital rectal exam (DRE) were normal (ie, negative family history of cancer, white patient), the average risk of finding cancer in this group is approximately 35\% on a single repeat biopsy.\textsuperscript{6} (The risk of cancer on biopsy in a 65-year-old white man with a prostate-specific antigen of 4.4, negative family history, normal DRE, and negative previous biopsy is 27.1\%. The same factors with an abnormal DRE result in a cancer risk of 48\%. If 60\% have a normal DRE, the overall average is 35.46\%.) However, in this study,\textsuperscript{5} the patients underwent annual biopsy over a period of 3 years until cancer was diagnosed. At each biopsy after the first, there was again a risk of cancer diagnosis.

The study by Taneja et al\textsuperscript{5} speaks to two issues in prostate cancer: is PIN truly premalignant, and in whom should we consider a rebiopsy? The first question is important for scientific strategies for prevention as well as for understanding prostate cancer pathogenesis. The second has tremendous implications, given that more than 1 million prostate biopsies are performed in the United States annually and PIN is found in approximately 10\%.\textsuperscript{7}
Although the molecular biology of prostate cancer suggests similar patterns of genetic alterations (allelic losses, loss of heterozygosity, chromosomal gain, and decreased telomere length), there are challenging observations from this study\(^5\) and others that would dispute the link between these two processes.\(^7\) First, the rate of cancer detection found in the trial (33.5\%) is not substantially different from what would be expected in a simple rebiopsy of patients without PIN on their first biopsy (35.46\%). Second, and perhaps more concerning, is that the overwhelming majority of cancers that are detected after a diagnosis of PIN are low grade. This is perhaps the greater concern, given that it is becoming clear that most of these patients who are ultimately found to have low-grade tumors will not die as a result of their disease. Importantly, detection of these tumors may well have a net disadvantage to the patient because he has to decide between repeated biopsies and examinations for decades, if he chooses active surveillance, or a significant risk of urinary, bowel, and sexual adverse effects, if he chooses active treatment. Instead of PIN as a target of prevention therapies, we would strongly encourage development of biomarkers that predict the development of high-grade tumors, the tumors that are most likely to lead to morbidity and mortality.

So what should we recommend for a patient with PIN on biopsy? We would discourage aggressive rebiopsy unless a risk assessment tool (such as the Prostate Cancer Prevention Trial Risk Calculator) suggests a high likelihood of a high-grade tumor that was missed on biopsy. In such a situation, it is reasonable to consider a high-fidelity magnetic resonance imaging study (eg, 3 Tesla magnetic resonance imaging with an endorectal coil) to identify regions of high risk for repeat biopsy.

Prostate cancer prevention remains a critically important strategy for the control of the burden of this disease. Given the enormous difference in the range of prostate cancer phenotypes, we must seek biomarkers that predict the lethal phenotype.

References