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- Prostatitis
- Prostatic Intraepithelial Neoplasia (PIN)

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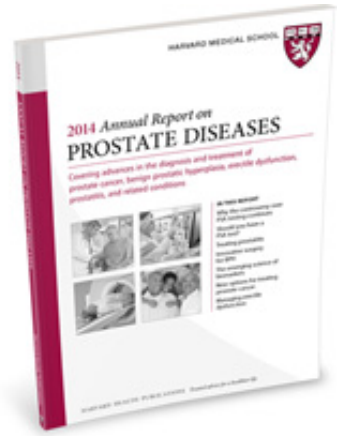

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What is prostatic intraepithelial neoplasia (PIN)?

In any given year, as many as 16% of men who undergo prostate biopsies will learn they have PIN, short for prostatic intraepithelial neoplasia. The simplest way to describe PIN is as a precancerous condition — but as is often the case in prostate disease, the situation is actually much more complex. First, only one type of PIN increases the risk of developing prostate cancer. And recent research indicates that the additional risk may not be as significant as originally thought.

Even so, a diagnosis of PIN presents men with a conundrum about what to do next. No consensus exists about what type of medical follow-up is in order or whether — and when — to treat PIN in the hopes of preventing prostate cancer. Moreover, the debate is about to become much more heated, because a drug to treat PIN is now undergoing phase III clinical trials, the last stage before submission to the FDA for approval. If the new drug is approved as a treatment for PIN, it's likely that it will be heavily promoted — adding a great deal of background noise to the debate about PIN.

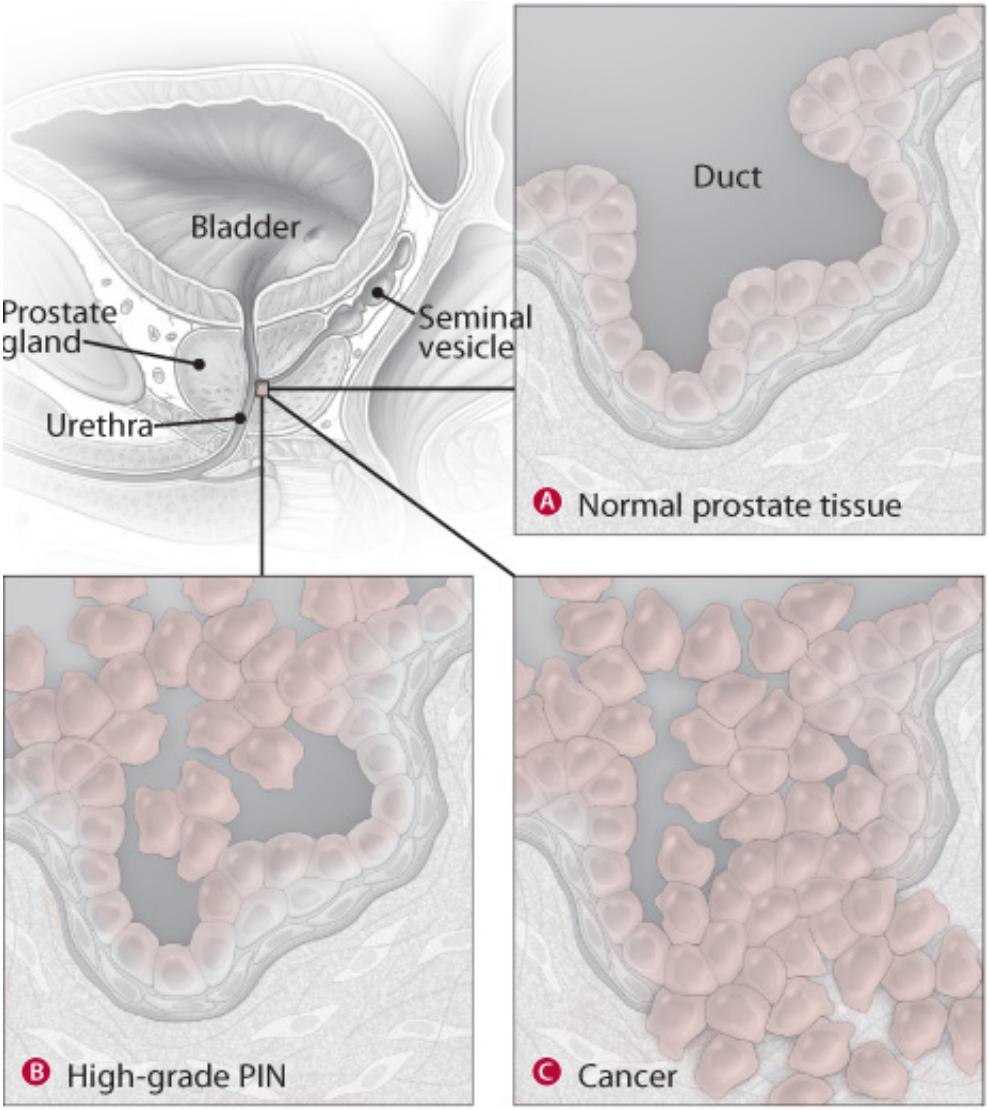
This article will help explain what PIN means, what your current options are if you are diagnosed with this condition, and what therapies are being investigated.

PIN: The basics

PIN is a condition in which some prostate cells have begun to look and behave abnormally. The abnormal cells are located in two areas: the lining of tiny sacs known as acini, which give the prostate its spongelike composition and produce fluid that is added to sperm to create semen; and the lining of the ducts that carry this fluid to the main ejaculatory duct that reaches the penis.

When PIN develops, the epithelial cells lining the acini and ducts become abnormal — but the lining itself remains intact (see Figure 1 below). In contrast, when prostate cancer develops, the epithelial lining is ruptured and the malignant cells penetrate into the tissue of the prostate gland itself. To further complicate matters, a related condition known as proliferative inflammatory atrophy (PIA) may also develop in the same area of the prostate, and may also increase cancer risk. (See "PIA: A related condition," below.)

Figure 1: Comparison of normal tissue, high-grade PIN, and cancer



Normal epithelial cells line the ducts (A) that carry fluid from the prostate gland to the main ejaculatory duct. In the case of high-grade PIN (B), the cells become abnormally shaped. Their nuclei, which contain genetic material, enlarge. Nucleoli, components of the nuclei that help build proteins, also enlarge and darken. Over time, these cells may become malignant and proliferate wildly, filling the duct and rupturing the epithelial lining (C). They can then penetrate into prostate gland tissue.

PIA: A related condition

Proliferative inflammatory atrophy (PIA) is another abnormality in the prostate that,

like high-grade PIN, is suspected of being a preliminary step in the development of prostate cancer. PIA involves inflammation and tissue degradation (or atrophy) in isolated areas of the epithelium — the same tissue affected by PIN. What's more, PIA typically develops in the peripheral zone of the prostate, the same area where PIN and most prostate cancers develop.

Researchers think PIA begins after an infection, toxin, or some other factor causes epithelial tissue in the prostate to atrophy or become inflamed. Cells in the affected area begin to proliferate faster than normal.

PIA has not been as well studied as PIN, so less is known about how much risk the condition confers. It is also not clear at this time if PIA leads to PIN, or if it represents an alternative pathway in the progression to cancer.

PIN is not detectable during a digital rectal examination (DRE), and does not raise PSA levels. The condition is usually diagnosed either during a prostate biopsy or when prostate tissue is removed during transurethral resection of the prostate (TURP), a treatment for benign prostatic hyperplasia.

Originally PIN was classified as grade I, II, or III, according to increasing degrees of abnormality. But in 1989, a consensus conference recommended simplifying this classification to differentiate between low-grade PIN (previously grade I) and high-grade PIN (grade II or grade III). The classification matters, because low-grade PIN does not increase your risk of developing prostate cancer, while high-grade PIN might.

But the diagnosis of high-grade PIN, which is based on a pathologist's reading of a given tissue sample, is subjective. Partly for that reason, it is unclear how many men can expect to be diagnosed with high-grade PIN in any given year. Studies of men who have undergone prostate biopsies have found that anywhere from less than 1% to more than 20% had high-grade PIN. A respectable ballpark estimate is that 4% to 8% of men who undergo prostate biopsies will be diagnosed with high-grade PIN.

There may be racial differences in the likelihood of developing high-grade PIN, although it is not known why — and few studies have examined the issue. One study reported that high-grade PIN occurs more often in African American men than in white men. An analysis of autopsies conducted in Brazilian men, some white and some of African descent, reported similar findings.

Progression to cancer

In low-grade PIN, the abnormal cells are only slightly different from normal cells. Moreover, studies indicate that someone whose initial biopsy reveals low-grade PIN has a risk of developing prostate cancer that is comparable to that of someone whose initial biopsy reveals normal tissue. Research has shown, for example, that a repeat biopsy will find cancer in about 16% of men with low-grade PIN, compared with roughly 20% of men with benign prostate tissue. However, your doctor may recommend a repeat biopsy even if you have low-grade PIN, for any one of a number of medical reasons. This is especially true if the physical exam or other tests reveal persistent abnormalities or other evidence of possible prostate cancer.

High-grade PIN presents a different situation, however. In high-grade PIN, the degree of cellular abnormality is more pronounced than in low-grade PIN. Several pieces of evidence also indicate that high-grade PIN is more likely to lead to the development of prostate cancer. First, high-grade PIN tends to arise in the peripheral zone of the prostate, which is where most cases of prostate cancer develop. Second, an autopsy study has shown that 82% of prostate specimens with cancer also had areas of high-grade PIN, while only 43% of those without prostate cancer did. Third — and probably most significant — most studies that have compared outcomes have found that men with high-grade PIN have an increased risk of being diagnosed with prostate cancer during a follow-up biopsy, when compared with men whose initial biopsies revealed low-grade PIN or normal tissue. However, it's also true that the more you look, the more you find: The detection of cancer on a follow-up biopsy is, to some degree, dependent on the number of times a biopsy is undertaken.

But just how great a risk high-grade PIN confers — and which men will actually go on to develop prostate cancer — is less clear. In part, this is because the complex series of steps that turn a normal prostate cell into a malignant one is not yet clear.

High-grade PIN is characterized by cells that share many genetic and molecular similarities with cancer cells. In high-grade PIN, the cell nucleus, which contains genetic material, is often enlarged, and particular components of the nucleus become abnormal — all of which may contribute to increasingly atypical behavior that can push the cells further down the path to malignancy. Over time, the abnormal cells may begin to proliferate excessively while becoming resistant to the programmed cell death that normally makes room for new cells by eliminating old ones. This is known as apoptosis. Sometimes referred to as cell suicide, apoptosis is an orderly and normal process of programmed cell death that the body relies on to replace old or

damaged cells with new ones. Malignant tumors grow partly because abnormal cells proliferate more than normal, but also because these cells somehow resist apoptosis. The result may be the out-of-control cell growth characteristic of cancer.

Although few studies have examined how quickly the progression takes place, one study of older men found that high-grade PIN preceded the development of cancer by 5 years, while a study of younger men found that it preceded cancer development by 10 years.

But here's the rub: High-grade PIN does not always progress to full-fledged invasive prostate cancer. In fact, the likelihood of progression does not appear to be as great as once feared. Most studies done in the early 1990s reported that about half of men with high-grade PIN were diagnosed with prostate cancer during a follow-up biopsy. But more recent studies report only a slightly elevated risk (see Table 1 below).

Table 1: Likelihood of progression to prostate cancer

High-grade PIN increases the risk of prostate cancer — but recent studies have found that the risk is not as great as once thought. In studies of men screened before 1995, high-grade PIN was estimated to more than double the risk of developing prostate cancer. In studies of men screened between 1996 and 2000, the risk was only slightly elevated.

Initial biopsy finding	**Percentage of men diagnosed with prostate cancer**	
	Repeat biopsy before 1995	Repeat biopsy between 1996 and 2000
Normal ("benign") tissue	19%	26.2%
High-grade PIN	51%	30.5%

Sources: *American Journal of Surgical Pathology* 1995;19:873–86. PMID: 7611534. *Urology* 2005; 65:538–42. PMID: 15780372.

Seven of nine studies found no increase in prostate cancer diagnoses in men whose initial biopsies revealed high-grade PIN, when compared with men whose initial biopsies showed normal tissue. (For more reading, see "Studies about high-grade PIN," below.)

Studies about high-grade PIN

Epstein JI, Herawi M. Prostate Needle Biopsies Containing Prostatic Intraepithelial Neoplasia or Atypical Foci Suspicious for Carcinoma: Implications for Patient Care. *Journal of Urology* 2006;175:820–34. PMID: 16469560.

Gokden N, Roehl KA, Catalona WJ, et al. High-Grade Prostatic Intraepithelial Neoplasia in Needle Biopsy as Risk Factor for Detection of Adenocarcinoma: Current Level of Risk in Screening Population. *Urology* 2005;65:538–42. PMID: 15780372.

Montironi R, Mazzucchelli R, Lopez-Beltran A, et al. Mechanisms of Disease: High-Grade Prostatic Intraepithelial Neoplasia and Other Proposed Preneoplastic Lesions in the Prostate. *Nature Clinical Practice Urology* 2007;4:321–32. PMID: 17551536.

This has left many doctors scratching their heads about how to advise patients diagnosed with high-grade PIN — and left patients wondering what to do. Men who learn they have high-grade PIN understandably want to do everything they can to avoid developing prostate cancer. But, unfortunately, consensus does not exist about what to do next, in terms of medical follow-up or intervention. And little is known about the "natural history" of high-grade PIN — in other words, what would happen if you did nothing.

Options for medical follow-up

Experts are divided about what type of medical follow-up to recommend — and for whom — when high-grade PIN is discovered on a first biopsy. Some doctors recommend using the standard prostate cancer screening tests — blood test for PSA, DRE, transrectal ultrasound, even family history of prostate cancer — to evaluate risk of progression. But a recent review of the research indicates these tests do not reliably help to identify which men with high-grade PIN will go on to develop prostate cancer. Likewise, no pathological features or molecular fingerprints have yet been identified that will enable doctors to distinguish high-grade PIN that is likely to progress from that which is not.

As a result, most of the debate in the medical field has centered upon how often a man

with high-grade PIN should undergo a follow-up biopsy to determine whether cancer has developed, and when such follow-up screening should begin.

The recommendations vary widely (see Table 2 below). Some doctors recommend a single follow-up biopsy in three to six months, or in 6 to 12 months, or at three years. Those who are hypervigilant might recommend multiple biopsies, done every three to six months for two years, and then annually for life.

Table 2: Your options after a diagnosis of PIN

Situation	Recommendations
A prostate biopsy reveals you have PIN.	• Ask whether it is low-grade PIN or high-grade PIN. • If it is low-grade PIN, no further testing or treatment is necessary. Low-grade PIN is virtually indistinguishable from benign tissue and does not increase the risk of prostate cancer. • If it is high-grade PIN, consider follow-up testing and treatment.
PIN is discovered during a TURP procedure (for benign prostatic hyperplasia).	• This is an incidental finding (one that occurs while doctors are looking for or treating something else). • If high-grade PIN is detected, a follow-up prostate biopsy is recommended to ensure that representative samples of the prostate are taken.
You need to decide when to have a follow-up biopsy after an initial finding of high-grade PIN.	• No consensus exists about the optimal timing of follow-up biopsies, or how many cores to sample. • If there are no other clinical signs of prostate cancer, such as an elevated PSA or abnormal DRE, you may want to wait at least a year to have a follow-up biopsy. • If your initial biopsy revealed atypical foci adjacent to the area of high-grade PIN, a second

	biopsy is recommended within three to six months. • Any follow-up biopsy should take samples from the entire prostate, not just the area where high-grade PIN was initially detected.
You are diagnosed with high-grade PIN and want to know what your treatment options are.	• Some studies suggest that androgen-deprivation therapy may help reverse high-grade PIN, but others do not. • Radiation therapy or prophylactic radical prostatectomy offer no benefits and carry significant risks. • Two promising chemopreventive agents are now being evaluated in phase III clinical trials: the nutrient selenium and the drug toremifene. Results should be available in the next few years. • Other clinical trials are evaluating the usefulness of fish oil supplements and a form of vitamin D.

In my view, undergoing multiple follow-up biopsies after high-grade PIN is detected is overdoing it. Here's why: One large study concluded that when PIN was diagnosed on an initial biopsy and then found again on a second biopsy, prostate cancer was more likely to be diagnosed in the future. But when the second biopsy was negative for PIN, the subsequent incidence of prostate cancer did not increase. One caveat, however, is that the reliability of such predictions is based on adequate biopsy sampling, so make sure your biopsy has least 12 cores.

The study analyzed the outcomes of nearly 25,000 men who entered a PSA-based prostate cancer screening program between 1992 and 2001. Researchers identified 190 men whose initial biopsies revealed high-grade PIN who then underwent at least one follow-up biopsy; 58 of these men eventually were diagnosed with prostate cancer. But the results of the first follow-up biopsy, when 25 (43%) of the 58 men discovered they had cancer, proved most predictive.

Of the 165 whose first follow-up biopsy did not reveal cancer, 27 had a finding of high-grade PIN. When the researchers tracked who later developed prostate cancer, they found that 41% of those with high-grade PIN on a first follow-up biopsy eventually developed prostate cancer, compared with only 18% of those whose first

follow-up biopsy showed benign findings. But subsequent follow-up biopsies did not have similar predictive power.

As mentioned earlier, the more you use biopsies to look for prostate cancer, the more you find it. But that does not mean it is the type that is going to become aggressive and life-threatening.

I agree with those physicians who recommend that men with high-grade PIN wait at least a year before undergoing a follow-up biopsy, provided that they have no other suspicious findings, such as elevated PSA or an abnormal DRE. It's important for men weighing the options to know that some studies suggest that 80% to 90% of prostate cancers are detected during the first repeat biopsy after a finding of high-grade PIN.

The caveat to this advice is that there is no one-size-fits-all recommendation for men with high-grade PIN. Your doctor may recommend multiple biopsies, done at frequent intervals, based on your overall prostate cancer risk profile — or your own comfort with that risk.

You may also get conflicting advice about how much of the prostate to sample, and what areas to sample. In my view, the biopsy should, at a minimum, sample at least 12 cores, taken not only from the area where high-grade PIN was detected, but also from other areas in the prostate. One study found that more than one-third of prostate cancers would have been missed if the repeat biopsy had sampled only the side of the prostate in which high-grade PIN had been discovered.

Other factors to consider

Increasingly, the research indicates that it is wise to consider other factors besides high-grade PIN when deciding what type of follow-up is necessary. Two situations in particular seem to increase the chances that high-grade PIN is a harbinger of prostate cancer.

One red flag is when high-grade PIN is detected adjacent to an atypical focus in the prostate gland (a small spot that looks suspiciously like cancer but can't be unequivocally diagnosed). In a study of men in this situation, more than half (an average of 53%) discovered they had prostate cancer during a repeat biopsy. For this reason, such men may want to consider undergoing a follow-up biopsy within three to six months.

Another red flag is when high-grade PIN is found in more than one location in the prostate gland (so-called multifocal high-grade PIN). Some research (but not all) has shown that this finding may also increase the likelihood of finding cancer during a repeat biopsy. It is not clear, however, how often men in this situation should undergo follow-up biopsies.

Current treatment options

At this time, experts do not recommend treating high-grade PIN. First, as discussed earlier, it's not clear that this condition will always progress to prostate cancer — and even when it does, it's impossible to predict which men will experience progression. Second, the current treatment options offer little benefit.

Androgen-deprivation therapy. Some studies of men with both high-grade PIN and prostate cancer who underwent treatment for the cancer have concluded that androgen-deprivation therapy reduced the extent of high-grade PIN. Yet other studies have found that this form of hormone therapy does not cause high-grade PIN to regress. It is not clear what accounts for these differences. In my own experience, androgen-deprivation therapy has little effect on PIN.

Finasteride (Proscar). Although the Prostate Cancer Prevention Trial showed that taking the medication finasteride (FDA-approved for the treatment of benign prostatic hyperplasia, or BPH) could reduce the risk of developing prostate cancer by nearly 25%, a study that looked specifically at this drug's impact on PIN found no effect, even after one year of therapy.

Other options. Radiation therapy has no effect on high-grade PIN. Removing the prostate gland surgically to avoid cancer development (prophylactic radical prostatectomy) is also not advisable, because it increases the likelihood of serious side effects such as incontinence and impotence — not to mention the risks of surgery itself.

What you can do now

If you are diagnosed with high-grade PIN, work with your doctor to determine the best management strategy for you. Because no consensus exists about the best medical follow-up, the first step is to evaluate your own risk profile to decide when a second biopsy should be scheduled. The findings of that biopsy will help clarify how great

your risk of developing prostate cancer really is.

Whatever you do, remember that finding out you have high-grade PIN is not the same as finding out you have prostate cancer. You have time to evaluate your options — and wait for new ones to develop.

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