

## PSA and Prostate Cancer

New England Journal of Medicine 2004;350:2239-46.

Journal of the American Medical Association 2005;294:66-70.

These publications examined the relationship between PSA and the risk of a diagnosis of prostate cancer if prostate biopsy were performed.

In the first of these two papers, a special study was performed on those men who participated in the PCPT who had a 7-year, end-of-study biopsy. This group of men was unique - virtually no one had examined the risk of prostate cancer in men with a level of PSA that was below 4.0 ng/ml- a level that was previously thought to be 'normal'.

The table below shows the risk of prostate cancer for ranges of PSA values. As can be seen, there is a risk of prostate cancer at all levels of PSA and this risk increases with PSA.

PSA ng/ml	Risk of prostate cancer	Risk of aggressive prostate cancer
<0.5	7%	1%
0.6 - 1.0	10%	1%
1.1 - 2.0	17%	2%
2.1 - 3.0	24%	5%
3.1 - 4.0	27%	7%

In the next paper, from the year 2005, the relationship between prostate cancer and PSA was examined throughout the range of PSA values - not just for men with a PSA less than 4.0 ng/ml.

Of 5587 men in the placebo group of the PCPT who all had a PSA and a prostate biopsy thereafter, the biopsy showed no evidence of cancer in 4362 while 1225 men (22%) were diagnosed with prostate cancer.

This study was conducted to help men and their doctors select the PSA level for which a prostate biopsy should be performed. It highlighted some important points: First, the higher the PSA value, the higher the risk of prostate cancer. Second, prostate cancer can be found even at low levels of PSA. Third, the higher the PSA level that is chosen to perform a biopsy, the greater the probability of prostate cancer but the greater the risk of missing prostate cancer at lower levels. Conversely, the lower the PSA level that is chosen to perform a biopsy, the more likely that a man with prostate cancer will be found but the more biopsies are required and the more likely that unnecessary biopsies will be performed.

The two measures that were used in this study were *sensitivity* and *specificity*. It is important to understand what these two measures mean. Sensitivity refers to the likelihood that, if cancer is present, the PSA test will be abnormal. This is a measure that

is most commonly of concern to both men and their doctors. A PSA value that is 90% sensitive will therefore be elevated in 90% of men with cancer. In general, if the goal is to find 95% of the cancers, a lower level of PSA will have to be selected.

Specificity is also an important measure of a test. Specificity is the likelihood that if you *don't* have cancer that your test will be normal. Because the risk of prostate cancer decreases with lower levels of PSA, in order to find more cancers if the level at which PSA is called abnormal is lowered, it will also cause more men who don't have cancer have an abnormal PSA and be recommended to have a biopsy. A PSA value that has a 90% specificity has a 10% risk of telling a man without prostate cancer that he needs a biopsy.

The table below shows the trade-off for PSA between sensitivity and specificity.

PSA	Cancer versus no cancer		Aggressive cancer versus all others
	Sensitivity	Specificity	Sensitivity
1.1	83%	39%	93%
2.6	40%	81%	67%
4.1	20%	94%	40%

This table shows the trade-off between cancer detection and risk of unnecessary biopsies for different levels of PSA.

Let's take the example of the 'traditional' level of 4.0 as the upper limit of normal of PSA. If this level is chosen, only 20% of all men who have prostate cancer would be recommended to have a biopsy. The advantage of selecting this level, however, is that of those men without cancer, only 6% would be recommended to have a biopsy. Looking at the more aggressive high-grade (Gleason grade 7 and higher) disease category, however, the results actually are better. A level of 4.1 would actually find 40% of those men with the more aggressive cancers. So, the historical level of 4.0 as an upper limit of normal for PSA works relatively well for a specific goal: minimizing the risk that a man without prostate cancer will be recommended to have a biopsy. It fails, however, in the primary goal of a cancer screening test: finding those men with cancer.

If we now look at the very low level of 1.1 for PSA and see how it does for cancer detection, it is clear that it works much better than the 4.1 level. This 1.1 PSA level would find 83% of those men with cancer and, in the far right column, actually finds 93% of those men with aggressive cancer. Unfortunately, lowering the PSA level to this point comes at a cost - 61% of those men without cancer would be recommended to have a prostate biopsy.

This new information has led some commentators to state that the PSA test "Fails" or "Isn't any good". Actually, the test is no different than other tests such as a measure of blood pressure or cholesterol. (A man with a 'normal' blood pressure or a 'normal' cholesterol does have a risk of having a heart attack. Just like PSA, however, the lower the value of each, the lower the risk of heart attack.) Using a sophisticated measure of

how the test performs, it actually does quite well when compared with other medical tests.

This information has helped physicians and men to better understand how the PSA test should be interpreted. Let's examine a few examples. A 60 year old man who is concerned about his risk of prostate cancer (he may have had a father with prostate cancer; he may be an African American man who has a higher risk; he may have had a next door neighbor who died of prostate cancer), now knows that his PSA of 3.5 isn't 'normal' but there is a risk that cancer may be present. A man who would like to be 40% certain that prostate cancer isn't present might then use a PSA of 2.6 to prompt a biopsy. A man who wants 90% certainty, might choose an even lower value. As this 60 year old man thinks about this, however, he must consider the risk that the biopsy is unnecessary - this risk increases with the lower value of PSA he chooses.

Men and their doctors, by virtue of the dedication of 18,882 men who participated in the PCPT, now have powerful new information to base their decisions on what level of PSA to perform a biopsy. In time, more information on risk will be available from this study.

(All percents in this section are rounded to the nearest whole number.)