Science Highlights

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To PSA or not to PSA: That is the Question.

The current raucous debate over the commonly used PSA blood test to screen for prostate cancer, the third leading cause of cancer deaths in men in the U.S.[(a)], stems from the U.S. Preventive Services Task Force's recommendation to discontinue PSA screening[(b)]. The debate is pitting physician against physician, cancer advocacy groups against health care insurance companies, and leaving men with enormous questions about what to do about their lifetime risk of developing prostate cancer.

The Task Force's recommendation is based on its review of medical literature that concluded that PSA screening leads to more unnecessary treatment complications than are justified by lives saved because of:

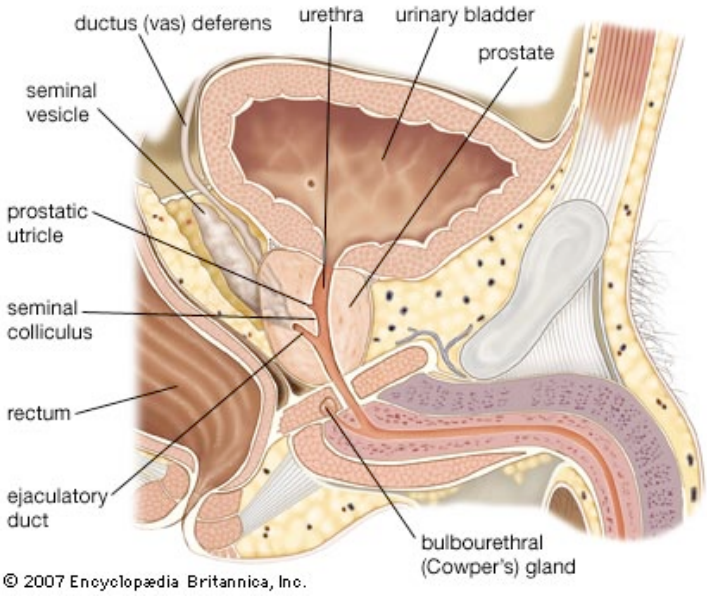
1. the questionable accuracy of the PSA test to detect cancer,
2. medical complications caused by unnecessary follow-up procedures because the PSA test has false positives, and
3. increasing pressures to slow the rate of increase of medical care

However, the well meaning conclusion by the U.S. Task Force to discontinue PSA screening is not likely to be followed by all physicians because of the negative consequences of missing a cancer if PSA screening is not performed.

A large European study has clearly demonstrated, however, that PSA screening reduces deaths from prostate cancer by 20%[(c,d)]. Therefore, until there are better options, PSA screening is unlikely to be abandoned, but the results need to be put in the context of individual prostate cancer risk and other medical indicators in order to minimize unnecessary invasive procedures. New guidelines for follow-up diagnostics and treatment need to be developed, and there is an urgent need for better prostate cancer screening

tests, like those being developed for semen specimens by Bedford Research Foundation scientists.

BACKGROUND



PSA is an acronym for “prostate specific antigen,” a protein made specifically by the prostate gland. The biological role of the prostate is to contribute fluids and proteins to semen at ejaculation. The other glands that contribute fluids and proteins to semen are the seminal vesicles. The prostate and seminal vesicles contract at ejaculation; the seminal vesicles contribute proteins that are extremely large, making semen thick, thus concentrating the sperm in the vagina, close to the cervix, the opening to the uterus. PSA is a specific type of protein, an enzyme, that is capable of breaking up the large seminal vesicle proteins, making them shorter and less viscous, allowing the sperm to swim free of the ejaculate, through the cervix into the uterus and fallopian tubes in search of an egg.

Another biological role for the proteins and fluids contributed by the prostate to ejaculated semen is to block negative responses to sperm by cells of the immune system in the vagina to protect the female reproductive organs from bacterial infection. Laboratory studies by Bedford Research scientists have shown that even very small amounts of semen added to cultures of immune cells causes them to die within 24 hours[(e)]. It seems possible that this suppression of immune response to protect sperm has the unwanted side effect of making the prostate gland itself “immune suppressed” and thus less capable of protecting itself from infections and cancer. Some men suffer from low grade infections of the prostate for years, a condition known as “chronic prostatitis.” Other men may also have chronic prostatitis, but without symptoms. Some studies indicate that chronic, low-grade infections can eventually lead to cancer.

Like most cancers, prostate cancer has several forms, many of which are so slow-growing that they are not life threatening -- not unlike a wart. Others are highly threatening because they grow very fast and invade surrounding tissues. The various types of prostate cancers are best distinguished by examination of small pieces of the prostate (biopsies) by a trained pathologist. Even then, it is sometimes difficult to distinguish fast growing from slow growing cancers, grouped under the general term “neoplasias” (“new growth”).

Because like other cancers, early prostate cancer can have no symptoms and not be detected during a physical exam of the prostate, the development of the PSA screening test in the late 1980's was greeted with enthusiasm as an additional tool to protect men from death by prostate cancer. Because it was a blood test, it was initially thought to predict cancer spread, beyond the prostate gland itself, into surrounding tissues, including the spine and the blood stream. It is now known, however, that cancerous prostate cells actually produce less PSA than normal prostate cells, so blood levels of PSA do not necessarily mirror tumor size or spread. A further complication of PSA screening is that many fast growing prostate cancers never lead to elevations in PSA levels. Moreover, chronic, low-grade infections, and the gradual increase in the size of the prostate gland that accompanies aging can also lead to elevated PSA in blood samples. The reason for this is unknown.

STUDIES CAUSING DEBATE

By the mid 1990's many studies to refine the use of PSA blood tests to predict prostate cancer had appeared. Some suggested following changes in PSA levels over time, some suggested isolating different forms of PSA in blood, e.g. "bound" or "free." But none of the refinements increased the specificity of the PSA blood test to distinguish prostate cancer from other diseases of the prostate, nor to always detect prostate cancer itself.

In March, 2009, the results of two large studies to determine the usefulness of testing blood samples for PSA were reported in the New England Journal of Medicine. The U.S. study*(f)* enrolled 76,693 men from 1993 to 2001: 38,343 to receive annual PSA screening and 38,350 to receive "usual care" to serve as the control group. Eighty six percent of the "annual PSA screening" group actually received annual screening for six years, and up to 52% of those in the "control group" also received annual PSA screening, markedly decreasing the power of the study to distinguish the long term effects of annual PSA screening after 7 to 10 years of follow-up. In contrast, the larger European study*(c)* enrolled 182,000 men in seven European countries (Netherlands, Belgium, Sweden, Finland, Italy, Spain and Switzerland) who were randomly assigned to receive PSA screening at an average of once every four years, or to receive no PSA screening. After an average of 9 years of follow-up, the death from prostate cancer in the screening group was 20% lower than in the control group. A more recent two-year follow-up to the original 9 years*(d)* confirmed that death from prostate cancer was 21% lower in the screening group at 11 years of follow up than in the control group.

Importantly, both the U. S and European study teams noted the high rate of complications and unnecessary surgeries resulting from both false-positive PSA screens, and highly invasive surgeries for slow-growing cancers that were in all likelihood not life threatening.

GOING FORWARD

That PSA screening prevents death from prostate cancer has been clearly demonstrated by the large European study. They are careful to note, however, that preventing death from prostate cancer did not influence "all cause mortality," suggesting no over-all lengthening of life span.

One way to prevent the complications and unnecessary surgeries that result from PSA screening is to not do it anymore, as has been recommended by the U.S. Task Force. Another way to prevent such problems is to adjust the responses of physicians and patients to the results of PSA screening. The panic that sets in at the mere thought of a cancer diagnosis needs to be treated first, before further diagnostics are initiated. Patients need to be able to keep in perspective the difference between a diagnosis of prostate cancer and the risk of dying from prostate cancer. The table illustrates the difference in the rates of death of the top five[(a)] cancers in men:

Estimated New Cancer Cases and Deaths in U.S. Men for 2012, All Races

Primary Site	Estimated New Cases in 2012	Estimated Deaths in 2012	Ratio of Deaths/New Cases
Prostate	241,740	28,170	0.12
Digestive System (esophagus to rectum, liver and pancreas)	156,760	80,560	0.51
Respiratory System	130,270	91,110	0.70
Urinary System (bladder and kidney)	97,610	19,670	0.20
Lymphoma and Leukemia	69,950	24,490	0.35

Cancer Facts & Figures, 2012, American Cancer Society; excludes basal and squamous cell skin

Having by far the lowest ratio of Deaths to New Cases emphasizes the slow growing nature of most prostate cancers. The aggressive U.S. campaigns to encourage people to get tested for cancer as a life-saving measure have been very successful, with many cancers detected at early enough stages for successful treatment. Bedford Research Foundation scientists are laying the groundwork for additional screening tools for early detection of prostate cancer in semen specimens.

But until new prostate cancer screening tools are developed and tested, it is time to launch a campaign about prostate cancer that emphasizes most are not life threatening, and overly-aggressive treatment of an elevated PSA screening test may cause life altering side effects far worse than living with the cancer itself.

References:

(a) National Cancer Institute, National Institutes of Health, American Cancer Society Cancer Facts and Figures, pdf

(b) Screening for prostate cancer. U.S. Preventive Services Task Force, 2008 (http://www.uspreventiveservicestaskforce.org/uspstf/uspsprca.htm).

(c) Screening and prostate-cancer mortality in a randomized European Study. N Engl J Med 2009;360:1320-8.

(d) Prostate-Cancer Mortality at 11 Years of Follow-up. N Engl J Med 2012;366:981-990.

(e) Seminal Plasma Induces Programmed Cell Death in Cultured Peripheral Blood Mononuclear Cells. Aids Res and Human Retroviruses, 2002,18:797-803. .pdf attached

(f) Mortality Results from a Randomized Prostate-Cancer Screening Trial. N Engl J Med 2009; 360:1310-1319.