NATIONAL CANCER INSTITUTE FactSheet

Prostate Cancer Research Results From the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

Key Points

- The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a large-scale clinical trial to determine whether certain cancer screening tests reduce the number of deaths from cancer. A biorepository of tissues and blood is being used for studies of markers of cancer cause and cancer risk.
- In the PLCO Trial, researchers are studying whether a digital rectal exam (DRE) and a blood test for prostate-specific antigen (PSA) will decrease the number of deaths due to prostate cancer. Men in the screening part of this trial undergo PSA and DRE testing.
- Initial results of the prostate screening part of the PLCO showed that six rounds of annual screening for prostate cancer, compared with community-based screening practices, led to finding more prostate cancers, but did not translate into fewer prostate cancer deaths up to 10 years after the start of screening.
- Studies using biorepository samples are locating new regions of the human genome linked to risk for prostate cancer.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, or PLCO, is a large-scale clinical trial to determine whether certain cancer screening tests reduce the number of deaths from these cancers. Screening for cancer may enable doctors to discover and successfully treat the disease earlier, preventing deaths. Together, these four cancers account for 40 percent of all diagnosed cancers in the United States and nearly half of all cancer deaths (45 percent). An estimated 255,980 people died of prostate, lung, colorectal and ovarian cancers in 2008.

Sponsored and run by the National Cancer Institute's (NCI) Division of Cancer Prevention, the PLCO Trial is taking place at 10 screening centers across the country: Denver, Colorado; Washington, D.C.; Honolulu, Hawaii; Detroit, Michigan; Minneapolis, Minnesota; St. Louis, Missouri; Pittsburgh, Pennsylvania; Salt Lake City, Utah (with a satellite center in Boise, Idaho); and Marshfield, Wisconsin.

Between 1993, when the trial opened, and 2001, when enrollment was completed, 154,942 women and men between the ages of 55 and 74 joined PLCO. Screening of participants

continued until 2006. Additional follow-up will continue for up to 8 more years to determine the benefits or harms of the cancer screening exams being studied.

The PLCO Trial also includes research on the genetic and environmental causes of cancer (prostate, lung, colorectal, ovarian, and other types of cancer) and studies of new methods for the early detection of cancer in collaboration with the NCI's Division of Cancer Epidemiology and Genetics and through the PLCO Biorepository.

Background on Prostate Cancer

Based on current U.S. rates, about 16 of every 100 men born today will be diagnosed with prostate cancer in their lifetime, while about 3 of every 100 men will die from this disease.

Although prostate cancer can occur in men of all ages, nearly 63 percent of cases are in men over age 65. Men are at greater risk if prostate cancer runs in their family, especially if a father or brother has had the disease. African American men are also at increased risk of prostate cancer, although researchers are not sure of the reasons. Some studies have shown that a diet high in fat may increase risk.

In the PLCO Trial, researchers are studying whether a digital rectal exam (DRE) and a blood test for prostate-specific antigen (PSA) will decrease deaths due to prostate cancer. A DRE is a physical exam where a health professional feels for abnormalities in the prostate gland. Because the prostate is located near the rectum, it can be felt by inserting a gloved finger into the rectum.

PSA is a protein produced by prostate cells, and PSA levels frequently are elevated in the blood of men with prostate cancer. The Food and Drug Administration (FDA) approved PSA screening for monitoring patients after prostate cancer treatment and for detecting prostate cancer in conjunction with DRE in men age 50 or over. However, it is still unknown whether PSA screening alone or in combination with DRE leads to a reduction in prostate cancer deaths.

Patient Population and Trial Design

The PLCO is a randomized, controlled trial in which over 150,000 persons 55 to 74 years old at entry were randomized to two study arms, half to undergo cancer screening (intervention group) and half to continue their normal health care routine (control group/community screening group). Both groups answer yearly questionnaires about their health.

The men in the intervention group undergo annual screening for prostate cancer with PSA testing and DRE. If a participant has a positive result from a screening test, the results are shared with the participant and his physician or a referral to an appropriate physician is made. The PLCO Trial design does not dictate the type of follow-up a person should have, although information on follow-up tests is collected.

Men in the screening arm of this trial undergo PSA testing and DRE upon entry. The men then have these tests annually for the next 3 years, and a PSA test without DRE in years 4 and 5. All PSA levels are analyzed by a single laboratory to ensure the quality and consistency of the

results. Participants in the intervention and control groups are contacted yearly for 13 years from the time they enter the study in order for the researchers to monitor their health.

Results/Publications

The following PLCO analyses regarding prostate cancer have been published, with the most recent studies listed first:

Screening and Related Clinical Studies

- **Six rounds of annual screening for prostate cancer compared with community-based screening practices led to finding more prostate cancers, but did not translate into fewer prostate cancer deaths up to 10 years after the start of screening.**

PLCO Trial data showed that six rounds of annual screening for prostate cancer led to finding 22 percent more prostate cancers by 7 years after the start of screening and 17 percent more prostate cancers by 10 years after the start of screening. Both groups had few deaths from prostate cancer, which is a reflection of good treatment practices in the United States and a healthy volunteer effect. The difference in the number of deaths between the groups is not statistically significant.

Of the men in the screening group, on average 85 percent had PSA tests and 86 percent had DREs each round. Annual random surveys of men in the usual-care group showed more men getting prostate cancer screening tests each year, up to 52 percent by the last year of trial screening.

Reference: Andriole GL, Grubb RL, Buys SS, et al. Mortality results from a randomized prostate-cancer screening trial. *New England Journal of Medicine* 2009; 360(13):1310–1319. Released online at http://nejm.org on March 18, 2009.

NCI News Release: http://www.cancer.gov/newscenter/pressreleases/PLCOProstateResults

- **Through four rounds of prostate cancer screening, most men in PLCO have followed the prostate cancer screening schedule. Compared with the baseline screening round, the positive predictive value of an abnormal PSA level (but not an abnormal DRE) decreased at subsequent screening rounds.**

The number of positive screening tests among the more than 38,000 men enrolled in the intervention arm of the PLCO has remained consistent during the 4 years of study. However, the positive predictive value of these tests—that is, the ratio of true positives to the total number of true and false positives—decreased over time from 17.9 percent at baseline to a range of 10.4 percent to 12.3 percent in subsequent annual screens. Researchers attributed this decrease to the fact that initial screening identified many of the cancers, leaving men with elevated PSA levels but negative biopsies to be identified in subsequent screening rounds. The cancers found at baseline were more likely than those found in subsequent screenings to be advanced stage (5.8

percent versus 2.9 percent) and to have a Gleason score of 7 to 10 (34 percent versus 25.5 percent).

Reference: Grubb RL, Pinsky PF, Greenlee RT, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Update on findings from the initial four rounds of screening in a randomized trial. *BJU International* 2008; 102(11): 1524–1530.

Earlier Study Results:

- **Both the rate of increase in PSA levels over time (PSA velocity) and PSA levels alone are significantly and independently associated with biopsy Gleason scores in men screened for prostate cancer annually who were diagnosed with prostate cancer. However, by studying men who later had prostatectomies as part of their treatment, these measures did not predict pathologic stage.**

Reference: Pinsky PF, Andriole G, Crawford, ED, et al. Prostate-specific antigen velocity and prostate cancer Gleason grade and stage. *Cancer* 2007; 109(8):1689–1695.

- **If a man had a prostate biopsy due to a positive cancer screening test, the chance of having a second biopsy within 3 years was 43 percent for men with suspicious PSA levels and 13 percent for men with suspicious DREs. The experience of this group of men should be generally representative of men undergoing periodic screening, and can provide context to the debate over optimum practice for repeat prostate biopsy.**

Reference: Pinsky PF, Crawford ED, Kramer BS, et al. Repeat prostate biopsy in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *BJU International* 2007; 99(4):775–779.

- **Prostate volume correlates both with PSA values and with the presence of benign prostatic hyperplasia (BPH). Using prostate volume estimated by DRE performed by trained examiners, PLCO investigators examined the relationship and found that both prostate volume and age were independently associated with PSA, but body mass index was not correlated to PSA values.**

Reference: Pinsky PF, Kramer BS, Crawford ED, et al. Prostate volume and prostate-specific antigen levels in men enrolled in a large screening trial. *Urology* 2006; 68(2):352–356.

- **The PLCO Trial is evaluating PSA- and DRE-based screening for prostate cancer in a clinically valid manner. Results of the baseline round of prostate cancer screening in the PLCO Trial show about 14 percent of men had either a positive PSA test or a positive DRE test. Of those men, about 12 percent were diagnosed with prostate cancer within 12 months, the majority with early-stage disease. The impact on prostate cancer deaths cannot yet be measured.**

Reference: Andriole GL, Levin DL, Crawford ED, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Findings from the

initial screening round of a randomized trial. *Journal of the National Cancer Institute* 2005; 97(6):433–438.

- **Men who receive a reproducible PSA test result of 7 ng/mL (nanograms per milliliter) or greater are more likely to have a subsequent prostate biopsy compared with men who have lower but still abnormal test results. The results were measured over 3 years. Men with a positive DRE without a positive PSA test were less likely to receive biopsy than men with a positive PSA test.**

Reference: Pinsky PF, Andriole GL, Kramer BS, et al. Prostate biopsy following a positive screen in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *Journal of Urology* 2005; 173:746–751.

- **A man's willingness to continue having prostate cancer screening tests is affected by a false-positive result on a previous prostate cancer screening and other measures. Men were significantly less likely to continue prostate cancer screening following a false-positive prostate cancer screening result. African American men and men with less than a high school education were also significantly less likely to receive further prostate cancer screening.**

Reference: Ford ME, Havstad SL, Demers R, Johnson CC. Effects of false-positive prostate cancer screening results on subsequent prostate cancer screening behavior. *Cancer Epidemiology, Biomarkers & Prevention* 2005; 14(1):190–194.

- **Many men who choose to get a PSA test may not need to repeat the test as frequently as previously thought. Almost 99 percent of men with a PSA value of 1 ng/mL or less will not see those levels rise to 4.0 ng/mL within 4 years. For men with an initial PSA reading of 1 to 2 ng/mL, nearly 99 percent would not see those levels rise to 4.0 ng/mL in 1 year.**

Reference: Crawford ED, Chia D, et al. PSA testing interval reduction in screening intervals: Data from the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. American Society of Clinical Oncology 38th Annual Meeting, Program/Proceedings, 2002.

- **In healthy male volunteers randomized to the screening arm within the PLCO Trial, race, age, and history of benign prostate disease are linked to variations in free (no longer bound to protein) and total (bound and unbound) PSA, but not percent free PSA. The differences are small and are of limited use in the clinical setting. However, since percent free PSA does not seem to be affected by race, this measurement may be useful when making comparisons across diverse groups.**

Reference: Gelmann EP, Chia D, Pinsky PF, et al. Relationship of demographic and clinical factors to free and total prostate-specific antigen. *Urology* 2001; 58(4):561–566.

Studies of Cancer Causes

Promising new technologies are enabling researchers to identify unique regions of human genes associated with a person's susceptibility to cancer. These technologies use single nucleotide polymorphisms (SNPs), the most common type of change in DNA (molecules inside cells that carry genetic information). SNPs occur when a single nucleotide (building block of DNA) is replaced with another, possibly causing disease.

Recent advances in human genomic research, including the development of technologies to search the human genome in a large-scale way using SNPs, make it possible to execute well-designed genome-wide association studies (GWAS). These studies of common genetic variations find the genes most often involved in cancer susceptibility. By scanning the DNA collected from men participating in the PLCO prostate cancer studies, NCI researchers have identified highly significant associations for prostate cancer risk with candidate SNPs.

- **Variation in the KLK genes, which code for PSA, are not associated with an increased risk of prostate cancer.**

This study explored the possibility that KLK3 and its encoded protein PSA may have a causal relationship with prostate cancer. The analysis of five case-control studies showed that SNPs in the KLK3 region were not associated with prostate cancer risk. Associations observed between the SNPs and prostate cancer risk may be due to the selection of subjects on the basis of PSA levels rather than a causal relationship with prostate cancer risk.

Reference: Ahn J, Berndt SI, Wacholder S, et al. Variation in KLK genes, prostate-specific antigen and risk of prostate cancer. *Nature Genetics* 2008; 40(9):1032–1034.

- **Fine-mapping analysis of prostate cancer susceptibility regions on human chromosome 8q24 creates a catalog for critical functional studies.**

Recently, GWAS have identified locations on chromosome 8 that are associated with the risk of breast, colon, and prostate cancers. At least three locations in a region known as 8q24 are independently associated with prostate cancer risk, one of which appears to be specific to certain populations. Previous research found two consecutive but independent locations in 8q24 that had a high potential to have relevant SNPs. In this study, researchers analyzed DNA samples from 39 prostate cancer cases and 40 controls of European origin using advanced sequencing technology. They were able to characterize a comprehensive catalog of common SNPs within 8q24, including 442 novel SNPs. The study generated a detailed map of genetic variation across this region of chromosome 8, creating a catalog for critical studies of the function of these SNPs.

Reference: Yeager M, Xiao N, Hayes RB, et al. Comprehensive resequence analysis of a 136 kb region of human chromosome 8q24 associated with prostate and colon cancers. *Human Genetics* 2008; 124(2):161–170.

- **Additional susceptibility loci identified in a genome-wide association study of prostate cancer implicate potential biomarkers for the disease.**

NCI researchers followed the initial GWAS of 527,869 SNPs on 1,172 individuals with prostate cancer and 1,157 controls of European origin nested in the PLCO Trial by testing 26,958 SNPs in four independent studies (total of 3,941 cases and 3,964 controls). Researchers confirmed and extended findings on chromosome 8 and other regions, as well as provided strong evidence for four novel associations and suggestive associations for an additional nine locations. On chromosome 10, one region corresponds to a gene that codes for a protein that is the primary component of semen and is a proposed biomarker for early detection of advanced prostate cancer. The region discovered on chromosome 7 contains a gene that may be related to endometrial cancer. On chromosome 11, researchers found a region of significance in a gene-poor region of the DNA, resembling the finding from May 2007 on chromosome 8. These findings suggest genetic variations in at least four regions of DNA that predict prostate cancer risk and that may be responsible for a large number of prostate cancer cases in white men in the United States. This finding may be used to develop further measures to identify men at high risk for prostate cancer and to prevent or diagnose the disease at an early stage.

Reference: Thomas G, Jacobs KB, Yeager M, et al. Multiple loci identified in a genome-wide association study of prostate cancer**.** *Nature Genetics* 2008; 40(3):310–315.

- **Chromosome 8 is found to have two independent areas that affect prostate cancer risk.**

Evaluating more than half a million SNPs in DNA from men in the PLCO Trial (1,172 men with prostate cancer and 1,157 men who did not develop the disease), NCI researchers identified a new association at chromosome 8q24 that conveys susceptibility to prostate cancer. This finding indicates the presence of at least two independent places in this region of chromosome 8 that contribute to the risk of developing prostate cancer in men of European ancestry. Based on combined analysis with four additional studies, there is compelling evidence that the span of DNA between these two markers in the 8q24 region contains a hot spot for genetic recombination.

Reference: Yeager M, Orr N, Hayes RB, et al. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. *Nature Genetics* 2007; 39(5):645–649.

NCI News Release: http://www.cancer.gov/newscenter/pressreleases/CGEMSprostateUpdate

Earlier Study Results:

- **Men's age, race/ethnicity, and tobacco and alcohol use are suggested risk factors for benign prostatic hyperplasia (BPH), a common condition in older men that shows increased risk for prostate cancer. Researchers confirmed that BPH increases dramatically with age; was lowest among Asians and consumers of alcohol; and tended to be lower among current cigarette smokers.**

Reference: Kang D, Andriole GL, Van de Vooren, RC, et al. Risk behaviours and benign prostatic hyperplasia. *BJU International*. 2004; 93:1241–1245.

# # #

Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 5.18, *Tumor Markers* (http://www.cancer.gov/cancertopics/factsheet/Detection/tumor-markers)
- National Cancer Institute Fact Sheet 5.23, *Early Prostate Cancer* (http://www.cancer.gov/cancertopics/factsheet/Detection/early-prostate)
- National Cancer Institute Fact sheet 5.27, *Interpreting Laboratory Test Results* (http://www.cancer.gov/cancertopics/factsheet/Detection/laboratory-tests)
- National Cancer Institute Fact Sheet 5.29, *Prostate-Specific Antigen (PSA) Test* (http://www.cancer.gov/cancertopics/factsheet/Detection/PSA)
- Prostate Cancer Home Page (http://www.cancer.gov/cancertopics/types/prostate/)
- Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Web Page (http://dcp.cancer.gov/programs-resources/groups/ed/programs/plco)
- *Understanding Prostate Changes: A Health Guide for Men* (http://www.cancer.gov/cancertopics/understanding-prostate-changes)
- *What You Need To Know About™ Prostate Cancer* (http://www.cancer.gov/cancertopics/wyntk/prostate)

How can we help?

We offer comprehensive research-based information for patients and their families, health professionals, cancer researchers, advocates, and the public.

- ***Call*** NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237)
- ***Visit*** us at http://www.cancer.gov or http://www.cancer.gov/espanol
- ***Chat*** using LiveHelp, NCI's instant messaging service, at http://www.cancer.gov/livehelp
- ***E-mail*** us at cancergovstaff@mail.nih.gov
- ***Order*** publications at http://www.cancer.gov/publications or by calling 1–800–4–CANCER
- ***Get help*** with quitting smoking at 1–877–44U–QUIT (1–877–448–7848)

This fact sheet was reviewed on 4/2/09