

## Colorectal Cancer Research from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: NCI Fact Sheet

### Key Points

- 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 death from cancer.
- In the PLCO Trial, researchers are testing flexible sigmoidoscopy. During a sigmoidoscopy, a thin, lighted viewing instrument is inserted into the rectum to examine the left, or distal, portion of the colorectum.
- The detection rate of colorectal cancer in subjects undergoing screening in one study was 1.8 per 1,000 in women and 3.8 per 1,000 in men, while the detection rate for advanced adenomas (pre-cancerous polyps) was 23 per 1,000 in women and 43 per 1,000 in men.

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 death from cancer. The PLCO is testing the effectiveness of early prostate, lung, colorectal, and ovarian cancer detection using the following tests: Digital rectal examination and blood prostate-specific antigen (PSA) testing for prostate cancer; chest X-ray for lung cancer; flexible sigmoidoscopy for colorectal cancer; and transvaginal ultrasound and the blood cancer antigen, CA-125, for ovarian cancer. Screening for cancer may enable doctors to discover and successfully treat the disease earlier, thus preventing deaths. Numerous epidemiologic and other studies are also part of this research.

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 United States: Birmingham, Ala.; Denver, Colo.; Washington, D.C.; Honolulu, Hawaii; Detroit, Mich.; Minneapolis, Minn.; St. Louis, Mo.; Pittsburgh, Pa.; Salt Lake City, Utah; and Marshfield, Wis.

Between 1993, when the trial opened, and 2001, when enrollment was completed, a total of 154,942 women and men between the ages of 55 and 74 joined PLCO. Screening of participants will continue until 2006. Additional follow-up will continue for at least 10 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.

Together, prostate, lung, colorectal, and ovarian cancers account for 42 percent of all diagnosed cancers in the United States and nearly half of all cancer deaths (47 percent). An estimated 266,360 people will die of prostate, lung, colorectal, and ovarian cancer in this country in 2005.

### Background on Colorectal Cancer

Colorectal cancer is the third most commonly diagnosed cancer among both men and women in the United States. Family history of the disease and a personal history of inflammatory bowel disease or polyps are factors known to increase a person's risk of colorectal cancer. A diet high in fat and low in dietary fiber also may increase a person's risk.



The colon and rectum are the lowest portion of the digestive system. The colon is the last five or six feet of the intestine and the rectum is the last eight to ten inches of the colon. Because the areas are connected, cancer researchers often report this as a single type of cancer.

In the PLCO trial, researchers are testing flexible sigmoidoscopy. During a sigmoidoscopy, a thin, lighted viewing instrument is inserted into the rectum to examine the left, or distal, portion of the colorectum. PLCO subjects with a polyp or mass noted on sigmoidoscopy are often referred for further examination with colonoscopy, a procedure that examines the entire colorectum.

### **Patient Population, Trial Design, and Data Collection**

The PLCO is a randomized, controlled trial in which 154,942 persons ages 55 to 74 at entry are randomly assigned to two study arms: Half to undergo cancer screening (intervention group) and half to continue their normal health care routine (control group). Both groups answer yearly questionnaires about their health and give biologic samples (blood and tissue) for studies of cancer causes and of early markers for cancer (biomarkers).

The sigmoidoscopy exam is offered twice—at the initial visit and at either the third or fifth annual visit, depending when the participant enrolled in PLCO. With the completion of enrollment and screening, researchers continue to follow participants in both groups for at least 13 years from the time they enrolled.

### **Results/Publications**

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

#### **Screening and Related Clinical Studies**

- **The PLCO trial offers a unique opportunity to examine the effectiveness of screening flexible sigmoidoscopy in a large, diverse population. Results from the initial screening and 12 months of follow-up were comparable to other studies.**

Of 77,465 subjects randomized to the screening arm, 64,658 (83 percent) received the baseline flexible sigmoidoscopy exam. A total of 18 percent of women and 28 percent of men were found to have a positive screen (i.e., a lesion or mass reported). The detection rate of colorectal cancer in subjects undergoing screening was 1.8 per 1,000 in women and 3.8 per 1,000 in men, while the detection rate for advanced adenomas (pre-cancerous polyps) was 23 per 1,000 in women and 43 per 1,000 in men. Because of the large size of the study population, the broad geographic representation, and the follow-up criteria, the results of the PLCO trial will offer a benchmark for screening flexible sigmoidoscopy in the United States.

Reference: Weissfeld JL, Schoen RE, et al. "Flexible Sigmoidoscopy in the PLCO Cancer Screening Trial: Results from the Baseline Screening Examination of a Randomized Trial." *Journal of the National Cancer Institute*. Vol. 97, No. 13. July 6, 2005.

- **Repeat screening flexible sigmoidoscopy three years after a negative exam will detect abnormalities or masses in the lower portion of the colon.**

The PLCO trial is evaluating the effect of flexible sigmoidoscopy (FSG) on colorectal cancer mortality. The trial screened the intervention group upon entry to the study and then in three years. Individuals included in this analysis had an initial FSG that showed no abnormalities or masses and then underwent a screening FSG three years later.

Of the 11,583 individuals without an abnormality or mass on initial FSG, 9,317 (80.4 percent) returned for repeat screening after three years. Of the people who returned, 1,292 (13.9 percent) had a polyp or mass detected. Of those with a polyp or mass, 951 (73.6 percent) went on to have follow-up screening, colonoscopy or repeat FSG. In the distal colon, 292 (3.1 percent) were found to have an adenoma (a pre-cancerous polyp) and 78 (0.8 percent) were found to have either an advanced adenoma or cancer.

Reference: Schoen RL, Pinsky PF, et al. "Results of Repeat Sigmoidoscopy 3 Years After a Negative Examination." *Journal of the American Medical Association*. Vol. 290, No. 1. July 2, 2003.

- **Data from the second screening for participants in the PLCO trial determined that excellent adherence to repeat screening with flexible sigmoidoscopy could be achieved. However, gender**

**may impact adherence to repeat screening, with women less likely to return for follow-up screening.**

This study was comprised of 10,164 patients from the PLCO screening trial who had a negative/normal initial screen. These patients were scheduled for repeat flexible sigmoidoscopy three years after the initial screening. Almost 87 percent of eligible patients returned for repeat screening.

Measures of nonadherence with repeat sigmoidoscopy varied significantly according to gender. Compared with men, women missed the year-three clinic almost two times more often than men, and women who attended the year-three clinic refused repeat sigmoidoscopy more than two times more often than men.

Reference: Weissfeld JL, Ling BS, et al. "Adherence to Repeat Screening Flexible Sigmoidoscopy in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial." *Cancer*. Vol. 94. 2002.

- **Overall, patients' thoughts are similar and positive for both CT colonography (virtual colonoscopy) and traditional colonoscopy, with less favorable thoughts about bowel preparation. Most patients state that they would prefer virtual colonoscopy for future evaluation.**

A newer examination for detection of colorectal abnormalities is CT colonography, or "virtual colonoscopy." Computer-simulated three-dimensional images are used to examine the mucosal surface of the colon and a two-dimensional view is used to visualize the structure of the colon. This non-invasive alternative offers several advantages to the patient over colonoscopy: No need for sedation or monitoring of vital signs and no recovery period. Disadvantages are that the conventional bowel preparation program is still needed and that the insufflation (blowing gas into the colon to enlarge the area) is uncomfortable.

A total of 120 patients were recruited for this study. The patients who were included had an increased risk of colorectal abnormalities due to suspected polyps, rectal bleeding, blood in the stool, history of prior polyps, or a family or personal history of colorectal cancer. These patients received virtual colonoscopy followed by a traditional colonoscopy on the same day.

The study showed that for both virtual colonoscopy and traditional colonoscopy, patients' thoughts after the procedure were more favorable than what was expected. Patients expressed more favorable thoughts about colonoscopy for pain and embarrassment with most responses being "none" to "a little" for both exams. Overall appraisals of the tests were favorable and similar between colonoscopy and virtual colonoscopy. Patients mainly expressed "not unpleasant" to "a little unpleasant." Overall appraisal of the bowel preparation was the most negative.

Reference: Ristvedt SL, McFarland EG, et al. "Patient Preferences for CT Colonography, Conventional Colonoscopy, and Bowel Preparation." *The American Journal of Gastroenterology*. Vol. 98, No. 3. 2003.

- **Subjects who have undergone screening flexible sigmoidoscopy (FSG) and were found to have non-advanced adenomas (pre-cancerous polyps) in the lower portion of the colon have a similar risk for advanced abnormalities in the upper portion of the colon as subjects with no adenomas in the lower colon. Subjects with advanced adenomas in the lower colon, however, are at an increased risk. Patients found to have these abnormalities were referred for a colonoscopy to examine the upper portion of the colon.**

Sigmoidoscopy is used to view the lower (distal) portion of the colon. When physicians find an abnormality in this area, studies have suggested that it is predictive of abnormalities in the upper (proximal) portion of the colon. Therefore, these patients are referred for a colonoscopy, which is able to view the entire colon.

A total of 8,802 patients underwent a full colonoscopy within one year of an abnormal baseline flexible sigmoidoscopy in PLCO, with two-thirds of those patients having a follow-up colonoscopy within three months. Subjects with advanced adenomas in the distal colon were found to be at increased risk for having advanced adenomas in the proximal colon; however, subjects with only non-advanced distal adenomas were not at increased risk for advanced proximal adenomas. Specifically, 12 percent of subjects with advanced distal adenomas, 4 percent of subjects with (only) non-advanced distal adenomas, and 4 percent of subjects with no distal adenomas were found to have advanced proximal adenomas.

Reference: Pinsky PF, Schoen RE, et al. "Predictors of Advanced Proximal Neoplasia in Persons with Abnormal Screening Flexible Sigmoidoscopy." *Clinical Gastroenterology and Hepatology*. Vol. 1. 2003.

- **In a group of patients who were found to have many polyps, radiologists were in agreement that virtual colonoscopy and traditional colonoscopy identified the same problems.**

The evaluation of computed virtual colonoscopy as a non-invasive examination of the colon continues to face new challenges. Early estimates of the diagnostic performance of virtual colonoscopy have been promising but variable.

The purpose of this study was to evaluate reader agreement by a radiologist for colorectal polyp detection in a group of patients who had many polyps. This group of patients, who were suspected of having polyps, was first examined with virtual colonoscopy and then traditional colonoscopy the same day. The images were analyzed independently by four experienced radiologists.

A total of 157 colorectal lesions ranging from 4 millimeters to 30 millimeters were found at colonoscopy and correlated with virtual colonoscopy findings. Overall analysis demonstrated a 75 percent agreement among the four readers.

Reference: McFarland EG, Pilgram TK, et al. "CT Colonography: Multiobserver Diagnostic Performance." *Radiology*. Vol. 225. 2002.

- **Approximately 70 percent of individuals who undergo screening sigmoidoscopy are satisfied and find the procedure more comfortable than expected, and only 15 percent to 25 percent find the procedure unpleasant. Physicians should not project discomfort to patients as a reason for not requesting screening sigmoidoscopy.**

Physicians often cite patient discomfort as a reason for not requesting sigmoidoscopy, but patient experiences have not been well-studied. The researchers for this study adapted a survey which was designed to measure satisfaction with screening mammography. Questions about screening using flexible sigmoidoscopy centered on convenience, accessibility, staff interpersonal skills, physical surroundings, perceived technical competence, pain and discomfort, expectations and beliefs, and general satisfaction.

A total of 1,221 patients were surveyed after sigmoidoscopy. The results show that over 93 percent of the participants strongly agreed or agreed that they would be willing to undergo another examination, and 74.9 percent would strongly recommend the procedure to their friends. Regarding pain and discomfort, 76.2 percent strongly agreed or agreed that the examination did not cause a lot of pain, 78.1 percent stated that it did not cause a lot of discomfort, and 68.5 percent thought that it was more comfortable than expected. Fifteen percent to 25 percent of the patients indicated they had a lot of pain, great discomfort, or more discomfort than expected. Women were more likely to have significant pain or discomfort than men.

Reference: Schoen RE, Weissfeld JL, et al. "Patient Satisfaction with Screening Flexible Sigmoidoscopy." *Archives of Internal Medicine*. Vol. 160. June 26, 2000.

- **Among experienced abdominal radiologists using virtual colonoscopy, the ability to find polyps was similar with 2-D and 3-D (two dimensional and three dimensional) display techniques, although individual cases showed improved results with 3-D display techniques. Evaluation of reader agreement (independent radiologists detecting the same abnormalities) demonstrated good agreement for 3-D display, but not as good for 2-D display.**

Virtual colonoscopy is a rapidly growing and evolving technology for the detection of colorectal polyps and permits viewing with 2-D and 3-D display techniques. This method is being used as a potential noninvasive alternative for the detection of colorectal polyps.

Virtual colonoscopy was performed on 16 patients who were suspected of having polyps at a prior flexible sigmoidoscopy examination or barium enema examination. Three specific 2-D and 3-D display techniques were tested. Three experienced abdominal radiologists independently analyzed each test case and each patient was retested six weeks later.

The results of readings 1 and 2 were similar for both 2-D and 3-D techniques among the readers. Overall observer agreement was good for the 3-D display techniques; however, observer agreement for 2-D techniques was lower.

Reference: McFarland EG, Brink JA, et al. "Spiral CT Colonography: Reader Agreement and Diagnostic Performance with Two- and Three-Dimensional Image-Display Techniques." *Radiology*. Vol. 218. 2001.

## Studies of Cancer Causes

- **Cigarette use is a risk factor for developing colorectal adenomas. Inherited variations in two genes (NQ01 and CYP1A1), which influence the activation of the cancer-causing substances in tobacco smoke, were found to increase risk for developing colorectal adenomas.**

In this study, researchers investigated the roles of variations in the CYP1A1 and NQ01 genes, combined with tobacco use, on the development of colorectal adenomas. These genes play a role in activating the cancer-causing substances in tobacco smoke. While tobacco use has been found to be a risk factor for developing colorectal adenomas, the role of these two genes is unclear. For this study, 772 people with at least one advanced adenoma and 777 people with no adenomas completed questionnaires about their lifestyles and had genetic tests done on their blood to determine if they had changes in these two genes.

The researchers found that the risk of having advanced colorectal adenomas was increased in smokers who had a variation in either the CYP1A1 gene or the NQ01 gene, and greatest in those with variations in both genes. In people who did not smoke, these gene variations did not affect their risk for developing colorectal adenomas.

Reference: Hou L, Chatterjee N, Huang WY, et al. "CYP1A1 Val<sub>462</sub> and NQ01 Ser<sub>187</sub> Polymorphisms, Cigarette Use, and Risk for Colorectal Adenoma." *Carcinogenesis*. Vol 26, No. 6. 2005.

- **Microsomal epoxide hydrolase (EPHX1) is responsible for breaking down carcinogens in cigarette smoke. Variations in this gene that increase EPHX1 protein activity appeared to increase risk for colorectal adenoma, particularly among recent and current smokers.**

Microsomal epoxide hydrolase (EPHX1) is a protein that breaks down polycyclic aromatic hydrocarbons found in cigarette smoke, which are known to cause cancer. However, in the process of breaking down these carcinogens, EPHX1 creates another carcinogen, benzo(a)pyrene 7,8 dihydrodiol 9,10 epoxide (BPDE).

Researchers looked at two variations in the EPHX1 gene that are thought to affect the level of activity of the EPHX1 protein. They compared 772 people with advanced colorectal adenoma to 777 people without the disease. Detailed information on smoking history was collected from a risk factor questionnaire that participants filled out when they enrolled in the PLCO study. Non-smokers were considered those who did not smoke cigarettes for more than six months or who did not smoke pipes or cigars for more than one year. Current or recent smokers were those who quit less than 10 years before enrollment in the study.

Researchers found that those participants with variations in the EPHX1 gene, which led to higher protein activity, had an increased risk of colorectal adenoma. This was especially true among recent and current smokers.

Reference: Huang W, Chatterjee N, et al. "Microsomal Epoxide Hydrolase Polymorphisms and Risk for Advanced Colorectal Adenoma." *Cancer Epidemiology, Biomarkers & Prevention*. Vol. 14, Issue 1. 2005.

- **Even though iron has been suggested as a risk factor for colorectal cancer, there was no relationship found between dietary intake of iron and risk of colorectal adenomas, the precursor condition to colorectal cancer. In addition, genetic variations that increase levels of iron in the blood were not found to be related to adenoma risk.**

Both iron intake and measures of iron in the blood have been suggested to be related to increases in the risk of colorectal cancer and adenoma. Researchers looked at iron intake and genetic variation in 679 people with advanced colorectal adenoma and 697 controls. Iron intake information was taken from participant responses to a food frequency questionnaire. Researchers found no relationship between iron intake and risk of adenoma.

Variations in the hemochromatosis gene (HFE) affects levels of iron in the blood. Researchers who looked at three different polymorphisms, or variations in this gene, did not find any relationship between the polymorphisms and risk of adenoma.

Reference: McGlynn KA, Sakoda LC, et al. "Hemochromatosis Gene Mutations and Distal Adenomatous Colorectal Polyps." *Cancer Epidemiology, Biomarkers & Prevention*. Vol. 14, Issue 1. 2005.

- **People who had a high calcium intake, greater than 1200 mg/d (milligrams per day), had reduced risk of colorectal adenoma, a pre-cursor condition to cancer.**

Calcium can reduce the risk of colorectal tumors by reducing exposure to harmful compounds in the bowel, or by influencing various cellular activities in the colon, such as cell growth and death. This study compared supplemental and dietary calcium intake of 3,696 people with adenoma to 34,817 controls. Calcium intake information was derived from individual responses on a food frequency questionnaire. Researchers found that people with the highest intakes of calcium had the lowest risk of colorectal adenoma. The association between intake and risk was stronger for calcium from nondairy foods and supplements, and for adenoma of the distal colon, the part of the colon farthest from the stomach.

Reference: Peters U, Chatterjee N, et al. "Calcium Intake and Colorectal Adenoma in a U.S. Colorectal Cancer Early Detection Program." *American Journal of Clinical Nutrition*. Vol. 80. 2004.

- **Variations in the calcium-sensing receptor gene were associated with advanced colorectal adenoma, a precursor condition to cancer. Also, a protective association was found between total calcium intake and advanced colorectal adenoma risk.**

The calcium-sensing receptor (CASR) is thought to mediate calcium's role in preventing cancer. Researchers looked at three common polymorphisms, or variations, in this gene in 772 people with advanced colorectal adenoma and 777 people without the disease. They found an association between advanced colorectal adenoma and these polymorphisms. This is the first study to evaluate variations in this gene in relation to risk of colorectal adenoma. Therefore, this study contributes new data that show a mediating role of CASR in preventing cancer.

This study also looked at calcium intake by reviewing participants' answers to a food frequency questionnaire which contained questions about dietary calcium intake and supplement use. A protective association was found for total calcium intake. For each additional 1,000 mg of calcium they took, participants had a 21 percent reduction in risk of advanced colorectal adenoma.

Reference: Peters U, Chatterjee N, et al. "Association of Genetic Variants in the Calcium-Sensing Receptor with Risk of Colorectal Adenoma." *Cancer Epidemiology, Biomarkers & Prevention*. Vol. 13, Issue 12. 2004.

- **The VDR TaqI variation in the vitamin D receptor gene was not associated with risk of advanced colorectal adenoma, a pre-cursor condition to cancer. One vitamin D metabolite, 1,25(OH)2D, was not associated with advanced adenoma risk. Another vitamin D metabolite, 25(OH)D, was inversely associated with advanced adenoma risk in women but not in men.**

Vitamin D may be involved in the prevention of colorectal cancer, and this action may be mediated by the vitamin D receptor (VDR). Researchers analyzed a polymorphism, or variation in the VDR gene, called VDR TaqI, in 763 people with advanced colorectal adenoma and 774 people without the disease. They found no association between this polymorphism and adenoma.

Researchers also measured blood serum levels of two vitamin D metabolites, 1,25(OH)2D and 25(OH)D, in a subset of 394 cases and 397 controls. They found that serum levels of 1,25(OH)2D were not associated with adenoma risk. However, for the second metabolite, 25(OH)D, researchers found that higher levels were associated with a decreased adenoma risk in women, but not in men. In women, when comparing those in the highest quintile with those in the lowest quintile, the risk of advanced adenoma decreased by 73 percent.

Reference: Peters U, Hayes RB, et al. "Circulating Vitamin D Metabolites, Polymorphism in Vitamin D Receptor, and Colorectal Adenoma Risk." *Cancer Epidemiology, Biomarkers & Prevention*. Vol. 13, Issue 4. 2004.

- **People who had a high level of fiber in their diet were at lower risk of colorectal adenoma, a pre-cursor condition to cancer.**

The potential impact of dietary fiber on colorectal cancer risk is controversial. Researchers examined fiber intake from food and supplements in 3,591 people with adenoma, and 33,971 people without the disease. They found that risk of adenoma decreased with increasing intake of dietary fiber in both men and women. People in the highest quintile of fiber intake, who consumed approximately 24 more grams of fiber per day than those people in the lowest quintile, had a 27 percent decrease in adenoma risk compared with those in the lowest quintile.

Reference: Peters U, Sinha R, et al. "Dietary Fibre and Colorectal Adenoma in a Colorectal Cancer Early Detection Programme." *Lancet*. Vol. 361. 2003.

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#### Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 5.31, Colorectal Cancer Screening (<http://www.cancer.gov/cancertopics/factsheet/Detection/colorectal-screening>)
- Colon and Rectal Cancer Home Page (<http://www.cancer.gov/cancertopics/types/colon-and-rectal>)
- Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Web Page (<http://dcp.cancer.gov/programs-resources/groups/ed/programs/plco>)
- Screening and Testing to Detect Cancer Home Page (<http://www.cancer.gov/cancertopics/screening>)
- *What You Need To Know About™ Cancer of the Colon and Rectum* (<http://www.cancer.gov/cancertopics/wyntk/colon-and-rectal>)

#### How can we help?

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