

Seminar article

The Prostate, Lung, Colon, and Ovarian (PLCO) cancer screening trial: status and promise

Gerald L. Andriole, M.D.^{a*}, Douglas Reding, M.D.^b, Richard B. Hayes, Ph.D.^c,
Philip C. Prorok, Ph.D.^c, John K. Gohagan, Ph.D.^c,
on behalf of the PLCO Steering Committee

^a *Division of Urologic Surgery, Washington University School of Medicine, Washington University in St. Louis, 4960 Children's Place, Campus Box 8242, St. Louis, MO 63110, USA*

^b *Marshfield Medical Research and Education Foundation, Marshfield, WI, USA*

^c *National Cancer Institute, Bethesda, MD, USA*

Abstract

The Prostate, Lung, Cancer, and Ovarian Cancer Screening Trial is a randomized, multicenter, study evaluating whether screening for prostate, lung, colon, and ovarian cancer will reduce cancer-specific mortality. More than 155,000 participants have been identified and will be monitored through 2015. A biorepository of screened individuals and control participants has been created. Together, the data derived from the intervention and control arms and material in the biorepository provide a valuable resource to allow identification and testing of novel biomarkers for human disease. © 2004 Elsevier Inc. All rights reserved.

Keywords: Cancer screening; Prevention; Biorepository

Introduction

The Prostate, Lung, Colon and Ovarian (PLCO) Cancer Screening Trial is a 23-year randomized trial in which more than 37,000 men will be screened for prostate, lung, and colorectal cancers and 37,000 women will be screened for lung, colorectal, and ovarian cancers. Prostate-specific antigen (PSA) and digital rectal exam (DRE; for prostate cancer), chest x-ray (for lung cancer), 60-cm flexible sigmoidoscopy (for colorectal cancer), and CA-125 blood test and transvaginal ultrasound (for ovarian cancer) are being investigated as screening modalities. An equal number of men and women will be followed up with routine medical care as controls. There will be a follow-up period of at least 13 years from randomization for both intervention and control participants to determine the effects of screening on cancer-specific mortality [1].

The PLCO trial provides a unique setting for the investigation of the etiology of cancer and other diseases and for the evaluation of potential molecular markers of early disease. At entry, baseline information is collected by questionnaire on

dietary intake, tobacco and alcohol use, reproductive history from women, family history of cancer, use of selective drug, and other selected risk factors. Blood samples collected at the baseline screen-exam are aliquoted to serum, plasma, red blood cell, and white blood cell (buffy-coat) fractions, and similar samples are reserved during upcoming annual screening visits. All blood samples are shipped to a central biorepository for long-term storage at -70°C . Dietary questionnaires and buccal cells for DNA analysis are obtained from nonscreened controls. Collectively, the structure of the PLCO trial with the integration of a centralized biorepository should allow the identification of novel etiological and biological aspects of human cancer [2].

Methods

The PLCO trial is a multicenter, randomized, two-arm trial designed to evaluate the effect of screening on cancer-specific mortality for prostate, lung, colorectal, and ovarian cancer. Randomization to the screened or control arm of the PLCO trial began in 1993 and concluded in 2001, with almost 155,000 men and women enrolled. Randomization and screening have been conducted at the following 10

* Corresponding author. Tel.: +1-314-362-8212; fax: +1-314-361-2203.
E-mail address: andrioleg@wustl.edu (G.L. Andriole).

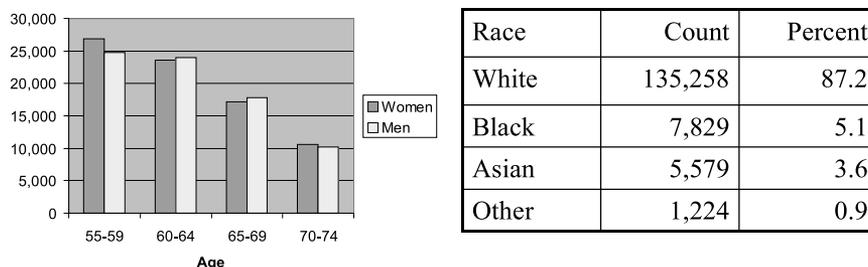


Fig. 1. PLCO baseline characteristics of enrolled participants.

screening centers: University of Colorado Health Sciences Center, Lombardi Cancer Research Center of Georgetown University, Pacific Health Research Institute, Henry Ford Health System, University of Minnesota School of Public Health/Virginia L. Piper Cancer Institute, Washington University School of Medicine, University of Pittsburgh/Pittsburgh Cancer Institute/Magee-Women’s Hospital, University of Utah School of Medicine, Marshfield (Wisconsin) Medical Research and Education Foundation, and the University of Alabama at Birmingham. All laboratory-screening tests are performed at a central facility located at the University of California at Los Angeles.

Men and women in the screened arm of the PLCO trial receive flexible sigmoidoscopy and chest x-ray. Men in the screened arm also receive DRE and PSA tests and women in the screened arm receive CA-125 and trans-vaginal ultrasound testing. The PLCO trial enrolled 55- to 74-year-old men and women who reported no previous personal history of prostate, lung, colorectal or ovarian cancer. Exclusion criteria included 1) current treatment for cancer except basal or squamous cell skin cancer; 2) previous surgical removal of the entire prostate, one lung, or the entire colon; 3) participation in another cancer-screening or primary prevention study; and 4) usage of finasteride [4-azaandrost-1-ene-17-carboxamide,N-(1,1-dimethylethyl)-3-oxo-,(5a,17b)] in the previous 6 months. Beginning in April 1995, the PLCO

trial also excluded men reporting more than one PSA blood test in the past 3 years, and men and women reporting any lower gastrointestinal procedure (proctoscopy, sigmoidoscopy, barium enema, or colonoscopy) in the past 3 years. Additional details about the design of the PLCO trial have been published elsewhere [3].

Using a baseline questionnaire administered before or soon after entering the study, subjects recorded personal sociodemographic characteristics (age, race, sex, marital status, education), family cancer history, personal medical history, cigarette smoking history, and cancer screening history within the past 3 years.

Baseline PSA tests are performed using a Hybritech Assay (Beckman-Coulter, San Francisco, CA). A PSA level greater than 4 ng/ml is considered suspicious for cancer. The DRE exams are performed by physicians, qualified nurses, or physician assistants, and the results are characterized as suspicious for cancer if there is nodularity or induration of the prostate or if the examiner judged the prostate as suspicious for cancer based on other criteria including asymmetry. Men with suspicious PSA or DRE results were notified of their results and advised to see their individual physicians for diagnostic follow-up. The PLCO trial obtains medical records related to diagnostic follow-up of positive screens and medical record abstractors recorded information on relevant diagnostic and treatment proce-

Exam Cycle	Risk Factors	Usual Diet	Serum	Plasma	RBC	DNA	Viable Cells	Tumor Sample
Intervention Arm								
Baseline	X	X	X	X	X	X		
Year 1			X					
Year 2			X					
Year 3		X	X	X	X	X		X
Year 4			X	X		X		
Year 5			X	X	X	X		
2004-2008	P							P
Non-intervention Arm								
	X	X				X		P

X: in place; P: Proposed

Fig. 2. Biologic materials and questionnaire data collections in the PLCO trial. (Color version of figure is available online.)

Table 1
Status of collections in PLCO

	Collections (n)	Completion year
General questionnaire	154,951	2001
Diet questionnaire #1	71,877	2001
Diet questionnaire #2	154,291	2004
Baseline blood	72,005	2001
Year 1 blood	70,664	2002
Year 2 blood	69,385	2003
Year 3 blood	68,202	2004
Year 4 blood	67,582	2005
Year 5 blood	66,889	2006
Buccal cells (control arm)	77,483	2004

dures. Certified tumor registrars are used to ascertain the stage, Gleason score, and type of all diagnosed cases of prostate cancer.

Baseline questionnaires

A general risk factor questionnaire is administered to all study participants at trial entry to elicit information on demographics, body build, history of selected medical conditions and treatments, cancer-screening history, family history of cancer, tobacco use, and occupation. Diet-related data are collected in a separate questionnaire, including information on usual consumption of foods, cooking practices, and use of nutritional supplements. To reduce costs, the questionnaires are self-administered and directly machine-readable. The individual screening centers are responsible for administering the questionnaire to screened participants, reviewing questionnaires for completeness, and sending questionnaires or the machine-read questionnaire results to a central processing facility for editing and merging with other trial data. An additional dietary questionnaire was added for screening arm participants in their fourth year on the trial and for control arm participants at trial entry. As the trial proceeds, additional questionnaires will be administered to screening and control arm participants to further elaborate on or to characterize changes in risk factor profiles.

Biologic sample collection

In addition to the blood collected for evaluation of PSA in men and CA-125 in women, additional blood is collected from screening arm participants for etiologic and early marker studies. At the baseline (T0) and subsequent screening exam, blood is collected and aliquoted into serum, plasma, red blood cell, and white blood cell (buffy coat) fractions. All blood samples (except the whole blood sample for cryopreservation) are shipped once per month on dry ice to the PLCO Biorepository at Frederick, MD, for long-term storage at -70°C . The blood samples for cryopreservation are shipped on the day of collection by overnight mail to the biorepository. Buccal cells are collected once from control participants [4].

Quality control

The overall management and structure for maintaining the quality of data and materials collected within the of the PLCO trial have been described elsewhere. Materials collection for etiologic and early marker studies is monitored at the screening centers and at the coordinating center. Questionnaires are usually reviewed for completeness. The general risk factor questionnaire includes a number of critical items that must be completed for each individual. During the processing of data, a series of checks are completed at the screening centers and centrally at NCI (Bethesda, MD), to assure exceedingly high standardization of follow-up clinical data on patients who have had screening tests. Each aliquot of blood is tracked through a computerized system that links sample collection, sample shipment, and sample storage. Progress in data and sample collection is reviewed on a monthly basis.

Results

A summary of certain demographic data for patients enrolled in the trial and a description of the composition of the biorepository is shown in Figs. 1 and 2, and Table 1, respectively.

Discussion

The PLCO trial is poised to answer important questions about the value of screening for prostate cancer. Moreover, the prospectively acquired biorepository will provide valuable information toward our understanding about the causes of cancer in humans. Etiologic and early marker studies may be carried out to address hypotheses concerning potential carcinogenic and anti-carcinogenic exposures and genetic susceptibility to disease risk. Questionnaire-based risk factors may be conducted, and biochemical and genetic studies of cancer etiology may similarly be performed. Studies to evaluate the natural history of disease and to characterize early markers may be conducted using the sequential collection of samples to relate biochemical changes in blood to the prediagnostic course of disease development.

References

- [1] Gohagan JK, Prorok PC, Hayes RB, Kramer BS, for the PLCO Project Team. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. *Controlled Clinical Trials* 2000;21: 251S–72S.

- [2] Hayes RB, Reding D, Kopp W, for the PLCO Project Team, et al. Etiologic and early marker studies in the Prostate, Lung, Colorectal and Ovarian (OLCO) Cancer Screening Trial. *Controlled Clinical Trials* 2000;21:349S–55S.
- [3] Prorok PC, Andriole GL, Bresalier RS, for the PLCO Project Team, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Controlled Clinical Trials* 2000;21:273S–309S.
- [4] Lum A, LeMarchand L. A simple mouthwash method for obtaining genomic DNA in molecular epidemiologic studies. *Cancer Epidemiol Biomarkers Prev* 1998;7:719–24.