Prevention and Early Detection Clinical Trials: Opportunities for Primary Care Providers and Their Patients

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**ABSTRACT**  Enrollment into cancer prevention and early detection clinical trials represents a unique challenge compared with a diagnostic or treatment trial because it involves subjects without a diagnosis of cancer. This paper examines some of the barriers to participation in prevention and early detection trials and provides detailed information about two ongoing prevention and two ongoing early detection clinical trials open to enrollment as well as brief summaries of seven additional trials now open to enrollment. (CA Cancer J Clin 2003;53:82-101.) © American Cancer Society, 2003.

**INTRODUCTION**

In the United States, cancer is a major source of disease burden, and the cost from morbidity and mortality is enormous in human and economic terms. Cancer is the second leading cause of death and the leading cause of premature mortality as measured by overall person-years of life lost. The National Cancer Institute (NCI) estimates that in 1999, Americans lost 8.3 million years of life as the result of premature death from cancer.1

Some progress is being made, which is evident in recent trends in cancer mortality. Data from 1999 show the death rates for all cancers combined continued to decline in the United States. However, the number of cancer cases can be expected to increase because of the growth and aging of the population in coming decades.2 Even in the presence of declining mortality rates, the importance of greater progress to reduce the burden of cancer is among the major scientific and public health challenges.

Years of scientific research have demonstrated that cancers occur not as sudden catastrophic events, but rather as the result of a complex and long-evolving process. The process of carcinogenesis can take decades to complete, providing time and opportunity to intervene to stop or to reverse its progress either before the clinical appearance of cancer or at its earliest stages. Due to the continuing burden, public health interventions have focused on prevention and early detection to reduce cancer incidence and mortality.

Logically, reducing cancer incidence through primary prevention is the most desirable goal, and early work by Doll and Peto3 suggested major reductions in cancer incidence are possible through improved nutrition, physical activity, and avoidance of tobacco products, the latter being the only strategy with demonstrated
efficacy and broad applicability. In addition to lifestyle factors, evidence suggests chemopreventive interventions and vaccines hold the greatest promise for reducing cancer incidence.

For some major cancers, early interventions after the detection of occult invasive disease, and in some instances precursor lesions, have been shown to offer significant advantages in reduced morbidity and mortality compared with treatment of disease after signs and symptoms are present.\(^4,5\) In the case of breast and colorectal cancer screening, randomized clinical trials have clearly demonstrated the benefits of screening, and there is sufficient inferential evidence to support screening for cervical cancer. Evidence also exists to support offering men the opportunity to make an informed decision about testing for early prostate cancer detection after a discussion about the potential but uncertain benefits and possible harms.\(^6-11\) While primary prevention, if possible, would be the overall preferred strategy, prevention and early detection at this time must be thought of as complementary strategies, i.e., reducing the burden of disease through prevention where possible and through earlier therapeutic interventions when prevention has failed or when a preventive strategy does not yet exist.

Early detection can also identify people who are at high risk for developing cancers because of the presence of precursor lesions, such as those with colorectal polyps or cervical squamous intraepithelial lesions. Such high-risk populations are frequently participants in prevention clinical trials. For some cancers, there are absolute genetic risks, such as Familial Adenomatous Polyposis, where people develop thousands of colorectal polyps. Clinical trials in these genetic risk populations also lead to identifying interventions that may have value in the general population.

PREVENTION AND EARLY DETECTION TRIALS:
THE PIVOTAL ROLE OF THE PRIMARY CARE PROVIDER

Among the various public health and clinical strategies that might be applied to reduce the burden of cancer in average- and high-risk populations, it is well accepted that recommendations to the public and health care professionals should be based on sound science. While the foundation for these studies normally arises from smaller investigations or observations from studies focused on different endpoints, ultimately the soundness of a potential prevention or early detection strategy depends on a demonstration of efficacy in a large prospective study capable of supporting a definitive statistical analysis of the results. These investigations tend to cost tens of millions of dollars and require many years of combined intervention and follow-up, and years of investigator and sponsoring agency time to measure the outcomes of interest. Usually these are studies that will never be repeated. This level of investment can be taken as a clear indication of the potential benefit to the public health if the intervention is effective. However, at the most fundamental level, the potential for the success of these studies depends on rapid enrollment of participants and their adherence with the study protocol.

Enrollment into prevention and early detection trials represents a unique challenge compared with a diagnostic or treatment trial because it involves subjects without a diagnosis of cancer. Once a person has been diagnosed with cancer, interest in beginning treatment and discussion of treatment options are paramount, and thus consideration of participation in a trial is more clearly relevant. However, for most individuals who are asymptomatic for cancer and in good health, unless a physician suggests they participate in a prevention study, they are likely to remain unaware of this option.
What are some of the barriers to participation in prevention and early detection trials? Research has shown physicians and individuals often lack awareness that studies are taking place in their communities. Physicians may fear losing control of their patient’s care, and likewise, individuals usually are unwilling to go against physicians’ advice or direction. If their doctor does not recommend a trial as an option for cancer prevention or early detection, they are unlikely to participate. Some physicians and many individuals are fearful, distrustful, or suspicious of research, and for many people the idea of being “randomized” to something other than the standard of care is simply unacceptable. For others, the possibility of being randomized to the current standard of care rather than to the new intervention being tested is unacceptable.

Individuals also face personal or practical obstacles, such as financial costs, time and travel, family considerations, and concerns about even temporarily leaving the care of their physician to participate in a trial. Likewise, today’s busy clinicians may not want to take the time or may not feel they have the time to identify and explain these study opportunities. Generalists have to be both knowledgeable and enthusiastic about seeking participation to make the effort needed for a successful referral to prevention and early detection studies.

Trial investigators must depend a great deal on the supporting role of the referring physician. Successful study accrual relies on collaboration among study investigators, the referring clinician, and the study participants. All participants receive, at least, the best standard treatment available. If a participant is taking a promising new agent or being screened with a new technology, they may be among the first to demonstrate benefit from the innovation. Many participants enjoy a sense of pride from their contribution to the advancement of medical knowledge that could improve care for others.

Below we describe two ongoing prevention and two ongoing early detection clinical trials open to enrollment. These studies address three of the leading cancers affecting men and women, specifically cancers of the lung, prostate, and breast. These three cancers represent the most common cancers affecting men and women, and each of these malignancies also is a major cause of death.

This year, the American Cancer Society (ACS) estimates 171,900 men and women will be diagnosed with lung cancer, and 157,200 will die of this disease.\(^{12}\) Not all lung cancer is caused by smoking, but the attributable risk from smoking is far greater than the combined attributable risks of all other risk factors known thus far. Even those who quit smoking remain at increased risk for lung cancer for a number of years; about half of all diagnosed lung cancers occur in former smokers. Although there is an obvious strategy to prevent this disease, i.e., not starting smoking or quitting, at present there are an estimated 90 million current and former smokers in the United States. Because thousands continue to take up smoking every day, at least for the next several decades a substantial number of individuals will be at high risk of developing lung cancer. If screening for lung cancer with newer technology proves to be efficacious, it could prevent tens of thousands of lung cancer deaths each year.

Prostate cancer is the second leading cause of death from cancer in men. In the United States, the ACS estimates that nearly 221,000 men will be diagnosed with prostate cancer in 2003, and approximately 29,000 will die from this disease.\(^{13}\) At this time, it is uncertain whether testing for early detection reduces prostate cancer mortality, although inferential data are suggestive of a benefit.\(^{9,10}\) However, even if screening does reduce prostate cancer mortality, as long as there are significant risks of side effects from therapy and an inability to distinguish incidental from life-threatening prostate cancers, it will be difficult to articulate with certainty an explicit disease control
Clearly, new disease control strategies, including an intervention for the prevention of prostate cancer, are a high priority.

Breast cancer is the most common cancer in women and the second leading cause of death from cancer in women. This year the ACS estimates 211,300 women will be diagnosed with breast cancer, and approximately 40,000 women will die from this disease. Screening for breast cancer has been shown to be effective in reducing mortality, but the current technology is imperfect and costly. Here again, primary prevention is preferable. However, improvements in early detection technology, which include new imaging technologies that address the fundamental limitations of conventional screen-film radiography as well as new technologies that are not based on imaging, are important areas for continuing investigation.

PREVENTION TRIALS

The Study of Tamoxifen and Raloxifene

The Study of Tamoxifen and Raloxifene (STAR) is a clinical trial to determine whether the osteoporosis drug raloxifene (Evista) has equivalent breast cancer risk reduction benefits, with a reduced risk of side effects, when compared with tamoxifen (Nolvadex) in postmenopausal women who are at an increased risk of developing the disease. Tamoxifen is the only drug approved by the US Food and Drug Administration (FDA) to reduce the incidence of breast cancer in women at increased risk, based on the 1998 results of the Breast Cancer Prevention Trial (BCPT), a study of more than 13,000 pre- and postmenopausal high-risk women aged 35 and older who took either tamoxifen or a placebo for up to five years. Women who took tamoxifen had a 50% reduction in the incidence of breast cancer compared with women on placebo. STAR is the follow-up trial to the BCPT.

STAR is funded primarily by the National Cancer Institute and coordinated by researchers with the National Surgical Adjuvant Breast and Bowel Project (NSABP). NSABP investigators are conducting STAR at more than 500 centers across the United States, Puerto Rico, and Canada (Figure 1).

About the Study Drugs

Both tamoxifen and raloxifene are Selective Estrogen Receptor Modulators (SERMs), agents that have estrogen-like activity in some tissues, but block the action of estrogen in others. For both tamoxifen and raloxifene, the antiestrogenic effects on breast cancer risk reduction apply predominantly to ER-positive breast cancer.

Tamoxifen has been used for more than 30 years to treat patients with breast cancer, and works, in part, by its interference with the activity of estrogen. In October 1998, the FDA approved tamoxifen to reduce the incidence of breast cancer in women at increased risk for the disease based on the results of the BCPT.

In December 1997, the FDA approved raloxifene for the prevention of osteoporosis in postmenopausal women. Raloxifene is being tested because large clinical trials of its effectiveness against osteoporosis have suggested that women at a low risk for breast cancer taking the drug developed fewer breast cancers than women taking a placebo.

Like most medications, tamoxifen and raloxifene cause adverse effects in some women. The less serious effects are often by women taking either drug are hot flashes and vaginal symptoms, including discharge, dryness, or itching. Treatments that may minimize or eliminate most of these side effects are available to the participants. Both drugs also have rare but serious side effects that can be life threatening.
Serious Side Effects of Tamoxifen

Tamoxifen increases the risk of two types of cancer that can develop in women with an intact uterus: endometrial cancer and uterine sarcoma. In the BCPT, women who took tamoxifen had more than twice the chance of developing endometrial cancer compared with women who took a placebo.\textsuperscript{14} The risk of endometrial cancer in women taking tamoxifen was comparable to the risk in postmenopausal women taking single-agent estrogen replacement therapy, about two cases of endometrial cancer per 1,000 women taking tamoxifen each year. In BCPT, all endometrial cancers that occurred in women taking tamoxifen were Stage I and were cured, suggesting that heightened surveillance for abnormal vaginal bleeding is important and may be an effective strategy for women who choose to take tamoxifen.

In 2001, the ACS issued new guidelines related to early detection of endometrial cancer in average- and high-risk women.\textsuperscript{18} The ACS recommended women at elevated risk for endometrial cancer from tamoxifen therapy should: (1) be informed about the risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians; and (2) be informed about the potential benefits, risks, and limitations of testing for early endometrial cancer detection in order to insure informed decisions.\textsuperscript{18}

Information collected by the FDA indicates that women who have used tamoxifen for breast cancer treatment or prevention also have an increased risk of developing uterine sarcoma.\textsuperscript{19} A review of all NSABP clinical trials using tamoxifen confirmed an increased risk of this rare cancer. In BCPT, there are about two cases per 10,000 women taking tamoxifen each year.\textsuperscript{20}
Research to date indicates that uterine sarcomas are more likely to be diagnosed at later stages than endometrial cancers, and may therefore be harder to control and more life threatening than endometrial cancer.

Women taking tamoxifen in BCPT had three times the chance of developing a pulmonary embolism as women who took the placebo, and were also more likely to have a deep vein thrombosis. Women taking tamoxifen also appeared to have an increased chance of stroke.

**Serious Side Effects of Raloxifene**

Information about raloxifene is limited compared with the data available on tamoxifen because of the shorter time it has been studied (about eight years) and the smaller number of women who have been studied. Studies of raloxifene have generally involved women who received the drug to determine its effect on osteoporosis, and the duration of both therapy and follow-up has been short. Women taking raloxifene in clinical trials have about three times the chance of developing a deep vein thrombosis or pulmonary embolism as women on a placebo. In osteoporosis studies of raloxifene, the drug did not increase the risk of endometrial cancer. An important part of STAR will be to assess the long-term safety of raloxifene versus tamoxifen in women at increased risk for breast cancer.

**Design and Eligibility**

Women at increased risk for developing breast cancer, who have gone through menopause and are at least 35 years old, can participate in STAR (Table 1). STAR is limited to postmenopausal women because the drug raloxifene has yet to be adequately tested for long-term safety in premenopausal women. All women must have an increased risk of breast cancer equivalent to or greater than that of an average 60- to 64-year-old woman. At that age, about 17 of every 1,000 women are expected to develop breast cancer within five years.

Increased risk of breast cancer is determined in one of two ways. The risk for most women...
is determined by a computer calculation based on the following factors:

- Current age;
- Number of first-degree relatives (mother, daughters, or sisters) diagnosed with breast cancer;
- Whether a woman had any children and her age at her first delivery;
- The number of breast biopsies a woman has had, especially if the tissue showed atypical hyperplasia; and
- The woman's age at her first menstrual period.

Women diagnosed as having lobular carcinoma in situ (LCIS) also are eligible based on that diagnosis alone, as long as any treatment for the condition was limited to local excision. A history of mastectomy, radiation, or systemic therapy would disqualify a woman with LCIS from the study.

Each potential participant will complete a one-page questionnaire (risk assessment form) that is forwarded to the NSABP by the local STAR clinical staff. The NSABP will use computer software to generate an individualized risk profile based on the information provided and will return the profile to the local STAR site so that it can be given to the potential participant. The profile estimates an individual woman's chance of developing breast cancer over the next five years and in her lifetime, and will also present her with the potential risks and benefits of the study drugs (described above). The woman can then use this information to help her decide whether she is interested in participating in STAR.

Health professionals at the STAR site will discuss existing health conditions that affect eligibility with each potential participant. For example, women with a history of cancer (except basal or squamous cell skin cancer), blood clots, stroke, or certain types of arrhythmias cannot participate; nor can those whose hypertension or diabetes is not controlled. Women taking menopausal hormone therapy cannot take part in the trial unless they stop taking this medication for three months. Women who have taken tamoxifen or raloxifene for no more than three months are eligible for the study, but they must also stop the medication for three months before joining STAR.

STAR is a double-blind randomized study. Participants in STAR will be randomized to receive either tamoxifen or raloxifene, and neither the participant nor her physician will know which she is receiving. All women in the study will take two pills a day for five years; half will take active tamoxifen and a raloxifene placebo, the other half will take active raloxifene and a tamoxifen placebo. All women will receive one of the active drugs; no one in STAR will receive only the placebo. The dosages of the active drugs are 20 mg of tamoxifen and 60 mg raloxifene.

The original sample size for STAR was estimated to be 22,000 women based on the minimum eligibility for study entry. The women who have joined STAR have, on average, had a greatly increased breast cancer risk, so the study sample size was reduced to 19,000. As of February 14, 2003, 15,390 women were enrolled in STAR or about 81 percent of the total.

Exams and Costs for Participants

Participants are required to have blood tests, a mammogram, a breast exam, and a gynecologic exam before they are accepted into the study. These tests will be repeated at intervals during the trial. Physicians’ fees and the costs of these medical tests will be charged to the participant in the same fashion as if she were not part of the trial; however, the costs for these tests generally are covered by insurance. The maker of tamoxifen, AstraZeneca, in Wilmington, DE, and the maker of raloxifene, Eli Lilly and Company, in Indianapolis, IN, are providing the active pills and the look-alike
placebos without charge. Every effort is made to contain the costs specifically associated with participation in this trial, and financial assistance is available for some women.

For More Information

To locate the nearest STAR center in the United States (including Puerto Rico) by phone, call the NCI’s Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The number for callers with TTY equipment is 1-800-332-8615. In Canada, participating centers can be located by calling the Canadian Cancer Society’s Cancer Information Service at 1-888-939-3333. Information about STAR can also be found on NCI’s Web site at http://cancer.gov/star on the Internet. Women who are interested in having their breast cancer risk assessed online and locating a STAR center near them can also use http://breastcancerprevention.com (a Web site of NSABP).

The Selenium and Vitamin E Cancer Prevention Trial

SELECT, the Selenium and Vitamin E Cancer Prevention Trial, is a clinical trial to determine if seven to twelve years of daily supplements of selenium and/or vitamin E reduce the risk of developing prostate cancer. SELECT is a necessary first step to substantiate earlier secondary endpoint findings from large prospective trials suggesting selenium and vitamin E reduce the risk of prostate cancer. Other objectives of the trial are to assess the impact of selenium and vitamin E on the incidence of lung and colon cancer as well as survival among individuals diagnosed with these diseases. SELECT will study the molecular genetics of cancer risk, associations between diet and cancer, assess age-related memory loss and quality of life.

The trial is funded by the NCI and coordinated by the Southwest Oncology Group (SWOG), an international network of research institutions.

About the Study Supplements

Selenium is a nonmetallic trace element present in water and food—especially seafood, meats, and Brazil nuts—that is an antioxidant believed to protect against the action of free radicals and prevent oxidative damage, limit the effect of a number of cell mutagens, and alter the metabolism of other carcinogens. In SELECT, the dose of selenium (provided as l-selenomethionine) is 200 micrograms (µg) daily. An earlier prospective trial by Clark, et al., designed to evaluate whether selenium could reduce the risk of nonmelanoma skin cancer, suggested that selenium might be an effective chemopreventive agent to reduce the risk of prostate cancer. The trial did not show a benefit from selenium in preventing skin cancer, but did show a 60% reduction in the number of new cases of prostate cancer in those men taking selenium compared with men who did not.

Vitamin E, a naturally occurring nutrient found in a wide range of foods—especially vegetables, vegetable oils, nuts, and egg yolks—is also an antioxidant believed to help control oxidative damage that can lead to cancer. The amount of vitamin E (provided as dl-alpha-tocopherol acetate) is 400 mg, which is equivalent to 400 International Units per day. In a 1998 study of 29,000 male smokers in Finland, those who took vitamin E to prevent lung cancer had 32 percent fewer new cases of prostate cancer than those who took the placebo.

Design and Eligibility

SELECT is a double-blind, randomized trial of 32,400 men divided into four intervention groups: (1) selenium and vitamin E; (2) selenium and a placebo; (3) vitamin E and a
placebo; and (4) two placebos. Enrollment began in August 2001 and will last for approximately five years, unless rapid accrual will reduce this period. The study will continue for seven years after enrollment is complete; men will participate for seven to twelve years, depending on when they join the study. More than 400 sites in the United States, Puerto Rico, and Canada are taking part in the study (Figure 2). As of January 31, 2003, 18,881 are enrolled or about 58 percent of the total needed for the trial.

To participate in SELECT, African-American men must be age 50 or older, and men of other races and ethnicities must be 55 or older (Table 2). Because African-American men develop prostate cancer at a younger age, they are eligible to enroll in SELECT at a younger age. Men who are taking selenium, vitamin E, or a multivitamin must stop using these supplements and use only what is provided by SELECT. Participants are provided supplements free of charge, including a multivitamin that does not contain selenium or vitamin E. Past use of selenium and vitamin E supplements does not disqualify men from joining SELECT.

Participants must be generally in good health and have no history of prostate or any other cancer except nonmelanoma skin cancer. Men with benign prostatic hyperplasia (BPH) can join SELECT; more than half of the men in the
United States between the ages of 60 and 70 and as many as 90 percent of men between the ages of 70 and 90 have symptoms of BPH.

Potential participants must have a digital rectal examination (DRE) that shows no signs of prostate cancer and a prostate-specific antigen (PSA) test level of less than or equal to 4.0 ng/ml. While enrolled in SELECT, DREs and PSA tests are suggested, but not required, on an annual basis.

Participant Costs

The supplements, placebos, and trial multivitamins are provided at no charge to SELECT participants. Physician, medical examination, and general clinic costs are charged to the participant in the same way as if he were not part of the trial. However, the costs of these tests may be covered by a participant’s health insurance. Financial assistance may be available for some men. Men with questions about insurance coverage or reimbursement should check with their local SELECT site.

For More Information

To locate the nearest SELECT center in the United States (including Puerto Rico) by phone, call the NCI’s Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The number for callers with TTY equipment is 1-800-332-8615. In Canada, participating centers can be located by calling the Canadian Cancer Society’s Cancer Information Service at 1-888-939-3333. Information about SELECT can also be found on NCI’s Web site at http://cancer.gov/select and at http://www.crab.org/select (the SELECT home page).
EARLY DETECTION TRIALS

The National Lung Screening Trial

The National Lung Screening Trial (NLST) is a cancer screening trial to compare two ways of testing for early lung cancer in current and former heavy smokers: spiral computed tomography (CT) and single-view chest x-ray. Both chest x-rays and spiral CT scans have been used in clinical practice to detect lung cancers in asymptomatic individuals as well as to evaluate signs and symptoms associated with lung cancer. So far, however, the scientific evidence is inconclusive as to whether screening for lung cancer with either method will reduce lung cancer mortality. NLST aims to determine which test will be better at reducing deaths from this disease and will examine the relative risks and benefits of both tests. Conducted by NCI, the trial will involve approximately 30 centers across the United States (Figure 3). Ten of the centers are those currently conducting the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), while the remaining 20 centers are members of the American College of Radiology Imaging Network (ACRIN). ACRIN is an NCI-funded cooperative group that manages clinical research trials of imaging technologies as they relate to cancer (for more information about ACRIN, visit http://www.acrin.org).

Design and Eligibility

Launched in September of 2002, the NLST is a randomized controlled trial and will enroll 50,000 participants over two years. The trial has sufficient power to detect a 20 percent or greater difference in lung cancer mortality between screening spiral CT and chest x-ray.
Participants are randomized to receive either a spiral CT scan or a chest x-ray on their initial visit, and two follow-up screens on an annual basis. Depending upon outcomes, researchers may contact participants by phone or mail at annual or semi-annual intervals until 2009 to monitor their health status and smoking behaviors. Some of the ACRIN sites are also collecting specimens of blood, urine, sputum, and resected tissue as part of a specimen biorepository that can be used to validate future potential biological and genetic markers of lung cancer. In addition, ACRIN sites will be addressing secondary endpoints related to costs, radiation exposures from screening, and the impact of screening on quality of life and smoking behaviors. All participants and their health care providers will be informed of the results of screening tests. Those with positive screening tests will be given suggested options for diagnostic follow-up based upon current state of knowledge practices that will be revised as new data become available during the trial.

Current or former heavy smokers between the ages of 55 and 74 may be eligible for this study (Table 3). Former smokers must have quit smoking within the past 15 years. Potential participants should be in general good health, must not have a history of lung cancer, and must not, in the past five years, have been treated for or have had evidence of any cancer, other than nonmelanoma skin cancer or most in situ cancers. Potential participants cannot be enrolled in any other cancer screening or cancer prevention trial other than smoking cessation studies and must not have had a CT scan of the chest or lungs within the prior 18 months. Participants who are current smokers and want to quit smoking will be referred to smoking cessation resources.

### TABLE 3

| National Lung Screening Trial (NLST) |
|--------------------------------------|
| **Objective** | The primary goal of NLST is to determine if lung cancer mortality is reduced in long-term or heavy current and former smokers by screening with low-dose helical computed tomography (spiral CT) compared with chest x-ray, and to determine the risk/benefit ratio of these tests. |
| **Sponsor** | National Cancer Institute. |
| **Coordinating Group and Lead Investigators** | National Cancer Institute via the Division of Cancer Prevention’s Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) Network and the American College of Radiology Imaging Network (ACRIN); John Gohagan, PhD, NCI Project Officer; and Denise Aberle, MD, ACRIN Principal Investigator/UCLA. |
| **Accrual Period/Sample Size** | September 2002 to September 2004; 50,000 participants. |
| **Accrual to Date/Participants Enrolled** | 13,279 as of February 10, 2003; 26 percent of total. |
| **Criteria for Participation** | • General good health.  
• Age 55 to 74.  
• Men and women.  
• Long-term or heavy smoker (30 pack-years).  
• Former smokers who quit within last 15 years.  
• No history of lung cancer. |
| **Total Sites** | 30 in the United States. |
| **Intervention** | Spiral CT or chest x-ray once per year for three years. |
| **Specimen Bank** | Division of Cancer Prevention: Under discussion–tumor tissue, blood collection.  
ACRIN: blood, urine, sputum, tumor tissue. |
| **Ancillary Studies** | In planning stages. |
| **Results/Findings** | Interim 2005 (Projected). |
| **For More Information** | Visit http://cancer.gov/nlst or call the National Cancer Institute’s Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). |
About the Tests

The sensitivity of chest x-rays is dependent on the size and location of the lesion, technical factors that influence image quality, and the skill of the interpreting physician. Lesions on the order of 20 mm diameter are commonly visible on chest radiographs, but may be missed for several reasons, including: (1) obscuration of the lesion by other chest anatomy (e.g., ribs, etc.), so called “structured noise;” (2) obscuration due to low contrast relative to surround, such as with lesions situated in the subdiaphragmatic or retrocardiac regions; (3) perceptual errors; and (4) satisfaction of search, meaning premature completion of image review based upon finding other less significant pathology. To date, trials of lung cancer screening with chest x-ray have provided insufficient evidence to conclude that chest x-ray is an effective screening tool, for which reason its potential is currently being evaluated in a large US trial.

Spiral CT, also called helical CT, and low-dose CT, also uses x-ray technology, but has much greater spatial and contrast resolution than conventional chest radiography, particularly for lesions within the lung. With spiral CT, the patient is moved continuously through a doughnut shaped scanner. The resulting x-ray data is a single volume of the whole chest, from which individual slices are reconstructed by a computer. With spiral CT, imaging times range from 10 to 25 seconds, typically the duration of a single, large breath-hold, and the volume data set enables both 2-D and 3-D reconstructions. Although low-dose CT involves roughly 10 to 15 times the radiation exposure of chest radiography, it is a more sensitive test for small pulmonary nodules, hence, its potential to detect lung malignancies at an earlier stage.

What the Current Data Tell Us About Lung Cancer Screening

The data currently being reported from the single arm observational trials using chest x-ray or spiral CT underscore some of the challenges of both technologies. The first report was issued from the Early Lung Cancer Action Project (ELCAP) and compared the use of spiral CT and chest x-ray in a screened cohort of 1,000 individuals at risk of lung cancer. In this study, all subjects received both imaging tests. The authors reported that low-dose CT significantly outperformed conventional chest x-ray in the detection of small pulmonary nodules. Low-dose CT identified 233 participants with noncalcified nodules. Of these, there were 27 lung cancers; 23 cancers were Stage I at diagnosis. In contrast, conventional chest x-ray identified 68 noncalcified nodules, of which seven were malignant and four were Stage I. The diagnostic work-up of positive CT screens was based on initial nodule size or change in size on repeat imaging. Based on the average tumor size in the ELCAP study, the authors project a five-year survival of 80 percent for cases diagnosed using low-dose CT.

The Mayo Lung Trial has also published its results in an initial cohort of 1,520 participants who have undergone baseline and annual incidence screening with spiral CT. They have observed that 51 percent or more of baseline screens and up to 14 percent of annual incidence screens are positive for lung nodules, of which over 98 percent represent benign nodules. Among 40 lung cancers diagnosed thus far, 21 (60 percent) have been Stage I at diagnosis. Thus far, eight participants have undergone surgery for the resection of benign disease.

These studies highlight some of the issues surrounding evaluating a screening test. First, albeit more sensitive than chest x-ray, spiral CT is nonspecific. The high false positive rate imposes the potential for psychological, economic, and medical hardship on individuals who must undergo additional diagnostic tests based upon the finding of a nonspecific lung nodule on CT, and the challenge to identify
best practices for minimizing adverse effects should not be neglected. Secondly, although lung cancers detected by CT are earlier stage than those detected with chest x-ray, it is not yet certain whether this apparent stage shift will result in a reduction in lung cancer mortality. We do not know, with measurable confidence, whether the detection of small lung cancers is tantamount to the detection of “early” curable cancers.

More than half of the hospitals in the United States have at least one spiral CT unit. While these machines are routinely used for diagnostic purposes in patients with unexplained signs or symptoms, recently some hospitals have begun performing spiral CT scans as a screening test in asymptomatic smokers and former smokers. A recent decision analysis by Mahadevia and colleagues was critical of this practice, since it promotes spiral CT in a manner that implies known effectiveness before definitive data are available, both in terms of efficacy, but also cost effectiveness. Although their modeling exercise showed that screening for lung cancer met conventional criteria for cost effectiveness when very modest mortality reductions were associated with very favorable estimates of screening program performance, their analysis also showed that under circumstances of less favorable performance, screening for lung cancer was not cost effective.

**Participant Costs**

Participants in the trial will be screened free of charge with either spiral CT or chest x-ray. However, the costs of any diagnostic evaluations or treatments for lung cancer or other medical conditions will be borne by the participants or their health insurance according to the provisions of their plan policies, in the same way as if they were not part of the trial. If a participant has no insurance, aid may be available at the local level to pay for diagnostic evaluation or treatment, and participants may be assisted in finding county or other regional medical resources for under- or uninsured individuals.

**For More Information**

To locate the nearest NLST study site or screening center, call the NCI’s Cancer Information Service toll free Monday through Friday, 9:00 AM to 4:30 PM, at 1-800-4-CANCER (1-800-422-6237) for information about the trial in English or Spanish. The number for callers with TTY equipment is 1-800-332-8615. Information about NLST can also be found at http://cancer.gov/nlst (NCI’s Web site).

**The Digital Mammographic Imaging Screening Trial**

The Digital Mammographic Imaging Screening Trial (DMIST) is a three-year multicenter study of digital mammography. Although screen-film mammography is still the “gold standard” for early detection of breast cancer, digital x-ray mammography may offer significant improvements. The primary aim of DMIST is the comparison of the diagnostic accuracy of digital mammography versus screen-film mammography for breast cancer screening. Secondary aims will address issues associated with the cost effectiveness of digital mammography and the impact of false positives on health-related quality of life issues. The study is sponsored by the NCI and is being conducted by ACRIN. DMIST was launched on October 29, 2001.

**Design and Eligibility**

DMIST is designed to compare the diagnostic accuracy of digital mammography versus screen-film mammography in women with no breast symptoms. The study will compare these two technologies with respect to their relative success in finding asymptomatic breast cancers.
Women who ordinarily undergo screening mammography at one of the 35 participating centers are eligible for participation in the trial. All eligible women are approached regarding their interest in participating in the trial at the time they are scheduled to be present for their regular screening mammogram. At this point, women are entered into the study and followed annually for two to three years (Table 4).

Women who are not eligible to participate in the study include those with a history of breast cancer treated with lumpectomy, a focal dominant mass or a bloody or clear nipple discharge, breast implants, any woman who is pregnant or has reason to believe she might be pregnant, and women who cannot, for any reason, undergo follow-up mammography at the participating institution or provide mammograms from another institution for review for one year after study entry.

After informed consent, all women will undergo both digital and screen-film mammography. Both studies are performed on the same day by the same breast-imaging technologist. As per local center protocols, two separate readers interpret the exams and the woman is informed of her results and, if applicable, the need for further work-up. For the majority of women, both tests are negative and only routine follow-up mammography is recommended. Each examination will be interpreted independently and work-up of any detected abnormalities will proceed based on the findings of either study. For those with abnormal mammograms, either digital or screen-film, further work-up takes place as recommended by the local radiologists. This includes extra mammographic views,
sonograms, magnetic resonance imaging and biopsy, as indicated. Women with benign biopsies are followed as recommended by the local radiologists.

Truth regarding breast cancer status for all patients will be determined either through the results of breast biopsy, if that occurs, or as a result of one-year follow-up. An expert breast pathologist will reinterpret all pathologic specimens. A total of 49,500 asymptomatic women presenting for screening mammography will be enrolled into the trial at 35 centers in the United States and Canada (Figure 4).

**About the Tests**

Conventional, screen-film mammography has been studied through many large randomized screening trials and has been shown to be associated with a reduction in breast cancer mortality of approximately 30 percent.6,36,37 These studies have been the basis for strong consensus that regular mammography beginning in the forties is an important part of women’s preventive health care.38,39 Modern mammography is performed on dedicated mammography systems that are optimized to provide a high quality, low-dose image of the soft tissues of the breast. The examination normally consists of two standard views of each breast, i.e., one mediolateral oblique (MLO) view and one craniocaudal (CC) view. However, this technology is not perfectly sensitive or specific, due partially because dense breast tissue can obscure lesions and the radiographic appearance of some histologic types. Further, a major limitation of screen-film mammography is film itself, since it serves as the medium of image acquisition, storage, and display. In addition, once a screen-film mammogram is obtained, the features of the image cannot be significantly manipulated. Contrast loss due to film underexposure, especially for dense glandular tissues, cannot be regained through manipulation of the image.
display. Improvements in visualization of lesion features require the acquisition of additional images, possibly with magnification or focal compression. This often requires a return visit by the patient, anxiety during the waiting period, and additional radiation exposure.

Digital detectors offer the prospect for improved detection because they provide better efficiency of x-ray photon absorption, a linear response over a wide range of incident radiation intensities, and low system noise. Digital acquisition systems directly quantify x-ray photons and decouple the process of x-ray photon detection from image display. Digital images can be processed by a computer and either printed to film or displayed on a
monitor. Since the steps of image acquisition and display are separated, each can be optimized. Because lesion conspicuity can be affected by contrast manipulations, it is believed digital mammography might improve breast cancer detection and breast lesion characterization. The ability to manipulate the image already has been shown to reduce the call-back rate for abnormalities that would require special views with conventional mammography, and investigators are optimistic that digital systems eventually will be more sensitive than screen-film systems used today.

Benefits, other than those predicted from the primary and secondary DMIST aims, also may result from digital mammography. First, the digital image capture will allow for the electronic transmission of images. This could enhance access to experienced mammographers from remote areas of the country or world that do not have direct access to mammography centers or trained mammographers. Electronic transfer of images would facilitate opportunities for breast imaging radiologists to consult with each other and aid in the training of future mammographers. Second, the digital images generated by digital mammography will provide a ready source of data that can be used in computer-aided detection (CAD) systems. In addition, image storage, transmission, and retrieval could be vastly more efficient compared with today’s hard copy images.
Possible Risks from Screening

The risks involved in this study are low. Women will receive a small amount of additional radiation beyond the amount they would normally receive with their standard mammogram. Also, because women are undergoing two imaging studies, there may be a greater risk of a false positive result that could cause anxiety and/or extra procedures to be performed.

Participant Costs

There is no cost to participants in the trial for digital mammography, and conventional mammography should be covered by the patient's insurance. The costs for any diagnostic evaluation would be covered by the participant's medical insurance according to the plan's policies.

For More Information

To locate the nearest DMIST study site, call the NCI's Cancer Information Service toll free Monday through Friday, 9:00 AM to 4:30 PM, at 1-800-4-CANCER (1-800-422-6237) for information about the trial in English or Spanish. The number for callers with TTY equipment is 1-800-332-8615. Information about DMIST can also be found at www.dmist.org and/or at http://cancer.gov/DMIST (NCI's Web site).

CONCLUSION

Well-designed, well-run clinical trials are the only way to determine the true effectiveness of a promising intervention. The four trials featured in this review were chosen to illustrate the importance and the potential benefit derived from such studies. For clinicians not familiar with the diversity of prevention and early detection studies currently accruing patients, we are including brief summaries of seven additional trials (Table 5). These include prevention studies for high-risk or average-risk patients and utilize a variety of nutritional interventions and drugs. In addition to NCI-sponsored trials, many cancer centers conduct smaller trials of early detection methods, and of pharmacologic, nutritional, and lifestyle interventions for cancer prevention.

To answer the most pressing questions about cancer—and to do so quickly—many more adults must participate in clinical trials. To encourage participation, the NCI, ACS, and other organizations provide information to ensure that health care professionals and the people in their care understand clinical trials, consider them as an option, and can easily locate them in their communities. Clinical trials should not be considered as opportunities only for people who already have cancer. They may also present prevention and early detection options for people at average and increased risk for developing cancer.

Ultimately, knowledge gained from prevention and early detection trials could have a vastly greater effect on reducing morbidity and mortality from cancer because the findings are applied to the entire at-risk population. In this era of evidence-based medicine, our progress toward identifying interventions and best practices will come faster and at a lower cost if clinicians and researchers can promote awareness of these studies, and play the essential role of aiding patients to make an informed decision about participation.

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