Literature Review

From:

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INTRODUCTION

Lung and colorectal cancers, the most common cancers in Americans, accounted for 46% of cancer deaths in males and 34% of cancer deaths in females in 1989 when this trial was being considered [1]. In males, prostate cancer was the third leading cause of cancer mortality and accounted for 11% of cancer deaths. In females, ovarian cancer accounted for 5% of cancer deaths. Mortality statistics for these cancers are similar today. In 2000, there will be an estimated 28,500 deaths among women and 27,800 deaths among men from colorectal cancer and, respectively, 67,600 and 89,300 deaths from lung cancer. About 14,000 women will die from ovarian cancer and 31,900 men from prostate cancer [2].

The death rate for prostate cancer has increased somewhat over time, while the rate for colorectal cancer has dropped, especially for females. The death rate for lung cancer has risen rapidly in both sexes, with a recent downturn for males [2]. Successful screening programs for these three cancers could have a major impact on overall cancer mortality. The death rate for ovarian cancer has remained relatively stable. Nearly 70% of ovarian cancers present as advanced disease with a poor prognosis, while localized disease has a 90% survival rate [3]. Successful screening might substantially reduce ovarian cancer mortality.

Uncertainty regarding the value of screening for these cancers has resulted in conflicting positions in the medical community and confusion in populations at risk. A randomized, controlled trial is necessary to determine the effects of screening on disease-specific mortality. The Prostate, Lung, Colorectal and

Ovarian (PLCO) Cancer Screening Trial is a 23-year randomized trial in which 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 examination (DRE) (for prostate), chest X-ray (for lung), 60-cm flexible sigmoidoscopy (for colorectal), and CA125 blood test and transvaginal ultrasound (TVU) (for ovary) are being investigated as screening modalities. An equal number of men and women will be followed 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 cause-specific mortality.

This paper describes the design of this trial at the completion of protocol development (just prior to the initiation of the pilot-phase recruitment) and protocol modifications that have occurred since. Included are the specific rationale for each cancer site, overall design features, screening and follow-up procedures, sample-size considerations, and data analysis plans. Recruitment into the pilot phase began November 16, 1993, with main-phase recruitment commencing September 30, 1994.

TRIAL RATIONALE

Prostate Cancer Screening

The DRE, the most common screening test for prostate cancer screening prior to 1990, has never been completely evaluated. Observational studies have examined sensitivity and case survival data, but without appropriate controls and with no adjustment for lead-time and length biases [4, 5].

In 1984, Chodak and Schoenberg [6] reported on 811 patients from 50–80 years of age who underwent rectal examination and follow-up. Thirty-eight of 43 patients with a palpable abnormality in the prostate agreed to undergo biopsy. The positive predictive value for prostate cancer was 29%. Forty-five percent of the cases were stage B, 6% stage C, and 18% stage D. More recent results from the same investigators revealed a 25% positive predictive value with 68% of the detected tumors clinically localized [7]. Others also reported a high proportion of localized disease when prostate cancer is detected by routine rectal examination [8–11]. In contrast, Wajsman and Chu [12] among others have reported that even with annual rectal examination, only 20% of cases are localized at diagnosis. Thompson and Zeidman [13] reported that 25% of men presenting with metastatic disease had a normal prostate exam.

A summary of the data on DRE for detection of prostate cancer concluded the following: sensitivity is 55–69%, specificity is 89–97%, positive predictive value is 11–26%, and negative predictive value is 85–96% [14]. Further, the rectal examination depends on the skill and experience of the examiner and the presence of a cancer in the posterior prostate. However, DRE is inexpensive, relatively noninvasive, nonmorbid, and can be taught to nonprofessional health workers. What remains to be determined is whether routine annual screening by rectal examination reduces prostate cancer mortality. A case-control study involving 139 men with metastatic prostate cancer and matched controls found the relative risk of metastatic prostate cancer to be 0.9 for men with one or more rectal examinations compared with men with none. The 95% confidence

interval was 0.5–1.7, suggesting that screening by routine DRE appears to have little effect in detecting and treating prostate cancer before it becomes metastatic [15].

Prostatic imaging by ultrasound, computerized tomography, and magnetic resonance imaging have also been suggested for prostate cancer screening. Each modality has relative advantages and disadvantages. Transrectal ultrasound has received the most attention [8, 16–22]. In a summary, Waterhouse and Resnick [23] reported that the sensitivity and specificity of ultrasound are too low for the procedure to be a valuable screening tool. Sensitivity ranged from 71–92% for prostate cancer and 60–85% for subclinical disease. Specificity ranged from 41–79%, and positive predictive values in the 30% range have been reported. The sensitivity and positive predictive value of ultrasound may be better than those of DRE when each is used as a single test. However, the relatively low specificity along with the invasiveness and cost of the procedure preclude routine screening for prostate cancer by transrectal ultrasound.

Serum PSA has been examined in several observational settings, both for initial diagnosis of disease and as a tool to detect recurrence after initial therapy [8, 20, 24–27]. Parameter estimates for this test include sensitivity near 70% and positive predictive values of 17–28%, although these estimates of predictive value are strongly dependent upon the disease prevalence in the populations studied [28]. The potential value of PSA lies in its simplicity, objectivity, reproducibility, lack of invasiveness, and lower cost relative to ultrasound. The test has increased the detection rate of early stage cancers, many of which may be curable by local therapy [9, 29, 30]. However, the test must be carefully evaluated because false positives in the form of benign prostatic lesions are common, requiring biopsies and added expense, and PSA testing cannot distinguish between latent or biologically irrelevant versus aggressive tumors.

The use of serial tests to assess the rate of change of PSA has been evaluated as a method to improve the specificity of the test [31]. The combination of PSA and ultrasound has been used to determine PSA density indexed to prostate size [32–34]. In one study, volume-adjusted PSA identified a population at higher risk of carcinoma [35], but another study of intermediate levels of PSA found no advantage to volume-adjusted PSA levels for screening [36]. Ratios of free to complexed PSA can amplify the differences in PSA levels for individuals with prostate cancer versus prostatic hyperplasia [37, 38]. No statistical advantage has been established for using the ratio of free to total PSA compared to total PSA alone in a screened population [39]; however, the free to total PSA ratio did improve specificity in other studies [40].

In a study by Cooner et al. [41] to resolve questions surrounding the relative merits of the three tests, all subjects had a rectal examination, PSA determination (Hybritech assay), and a 7-mHz ultrasound examination. Most of the participants with positive results on ultrasound plus a few other individuals were biopsied. The pertinent findings of this study and a similar study by Lee et al. [20] are given in Table 1. Both studies demonstrate that the rate of cancer among subjects with positive results on ultrasonography in whom the rectal and PSA exams are normal is extremely low. Hence, ultrasound was not included as one of the screening tests in this trial.

Careful evaluation of prostate cancer screening is mandatory because the natural history of the disease is variable and appropriate treatment is not clearly

Table 1 Effect of Rectal and Prostate-Specific Antigen Examinations on Cancer Rate in Patients with Abnormal Rectal Ultrasound

	Cooner Study			Lee Study		
	Biopsies	Cancer	Rate	Biopsies	Cancer	Rate
Rectal +, PSA +	235	151	0.64	89	63	0.71
Rectal +, PSA −	166	23	0.14	23	6	0.26
Rectal −, PSA +	134	41	0.31	92	31	0.34
Rectal −, PSA −	177	12	0.07	44	2	0.05

PSA = prostate-specific antigen.

defined [28, 42, 43]. The incidence of prostate cancer found at autopsy steadily increases for each decade after age 50, and most of these lesions are clinically latent. Some progress has been made in predicting the biologic behavior of these tumors, but despite improved understanding of the relationship among histologic grade, tumor volume, and biologic behavior, it is difficult to determine appropriate therapy for any given tumor [44]. A meta-analysis indicated that patients with low-grade prostate cancer can experience long-term survival with deferred therapy [45]. Decision analyses produce indeterminate results because of uncertainty regarding treatment efficacy and metastatic rates for prostate cancer [46–48]. On the other hand, a review of 60,000 cases of prostate cancer diagnosed between 1983 and 1992 showed that men with poorly or moderately differentiated cancer had improved survival if treated rather than followed [49].

Screening and treatment of a large population of males could entail substantial risks and morbidity, which include urinary incontinence, urethral strictures, sexual impotence, rectal injury, and a small probability of treatment-related mortality [44, 50]. Given these circumstances, careful evaluation of prostate cancer screening is needed. Currently, there is insufficient evidence with which to decide the efficacy or effectiveness of screening asymptomatic men [44, 47]. In addition to the PLCO trial, randomized trials are underway in other countries to address these issues [51, 52].

Lung Cancer Screening

Evaluations of chest X-ray and sputum cytology, the most common screening tests for lung cancer, were first reported nearly 30 years ago. The early studies include the Philadelphia Pulmonary Neoplasm Research Project [53], a nonrandomized, uncontrolled study begun in 1951; the Veterans Administration study [54], a nonrandomized, uncontrolled study performed from 1958 to 1961; the South London Lung Cancer Study [55], a nonrandomized, uncontrolled study done in 1955 to 1963; the North London Cancer Study [56, 57], a randomized study with industrial firms randomized between screening and no screening done in the early 1960s; and the Kaiser Foundation Health Plan multiphasic screening trial [58, 59], a controlled trial with annual chest X-ray, spirometry, and medical questionnaire as part of the multiphasic screening begun in 1964. None of these studies demonstrated a significant impact of screening on lung cancer mortality. The South London study, for example, showed an increase

in the survival of screen-detected cases compared with other cases found in the same geographical region, but without adjustment for self-selection bias, lead-time bias, overdiagnosis bias, or length bias [60, 61]. These studies typically were small, and for most, follow-up was short, so that any small to moderate size effect or any long-term effect was not likely to be demonstrated.

More recent studies include a randomized trial in Czechoslovakia [62, 63], a case-control study in the former German Democratic Republic [64], and a case-control study in Japan [65]. As with some earlier studies, the randomized groups in the Czechoslovakian study were screened with cytology and X-ray at two frequencies, semiannual versus every 3 years, so that there was no unscreened control group. There was no difference in mortality between the two groups. The German case-control study evaluated chest X-rays originally used for control of tuberculosis. The Japanese case-control study considered X-ray histories among deceased lung cancer cases and matched controls. In contrast to the German study, the odds ratio of dying from lung cancer for those screened within 12 months versus those not screened was 0.72, suggesting some benefit from the screening.

Three other randomized controlled trials have been conducted. One trial, the Mayo Lung Project, was initiated in 1971 for males 45 years or older who were heavy smokers [66–68]. Participants free of lung cancer on initial screening were randomized either to a group offered screening with sputum cytology and chest X-ray every 4 months or to a group not offered screening but advised to seek it annually. In the studies at the Johns Hopkins University Hospital [69–72] and at Memorial-Sloan Kettering Cancer Center [73, 74], intervention and control groups were offered annual chest X-ray, while the intervention group was also offered sputum cytology every 4 months. In the Mayo Clinic study, cases found in the screened arm were diagnosed in earlier stages than those in the control arm. However, there was no significant reduction in lung cancer mortality between the screened group and the control group in any of these trials.

Therefore, at this point there is no solid evidence that screening for lung cancer can reduce lung cancer mortality. Sputum cytology has not been shown to be effective as an adjunct to annual chest X-ray. There is evidence that screening with chest X-ray plus sputum cytology does improve stage at diagnosis and case survival rate relative to cases diagnosed through usual care, but despite this there was no reduction in lung cancer mortality. However, modeling using data from these trials suggests that there may have been as much as an 18% mortality reduction in these trials [75–77].

The Mayo study is the only one of the three which is pertinent to studying annual X-ray in the present trial because the use of screening X-rays differed in the two arms. However, several reservations can be noted about the Mayo study finding. First, the study was designed to detect a 50% reduction in lung cancer mortality and was too small to demonstrate a lesser but important reduction of 10–15%. Second, at the time the study was terminated there were still 40 excess cases of lung cancer in the screened group. Whether these cases represent overdiagnosis or a screening benefit that would only be seen with longer follow-up is not known. Third, about 50% of the men in the control group received an annual chest X-ray [68]. Thus, the level of contamination may have been sufficient to obscure any small to moderate benefit. Finally,

Table 2 Power to Detect Various Screening Effects in Previous Studies of Chest X-Ray Screening for Lung Cancer (Based on Actual Deaths Observed)

	Mortality Reduction (%)				
Study	10	20	30	40	50
Philadelphia	0.14	0.32	0.59	0.85	0.98
VA	0.16	0.38	0.69	0.92	0.99
South London	0.14	0.31	0.57	0.83	0.97
North London	0.16	0.39	0.70	0.93	0.995
Kaiser	0.12	0.27	0.50	0.76	0.94
Czechoslovakia	0.16	0.39	0.71	0.93	0.996
Mayo	0.21	0.54	0.88	0.99	0.999

when prevalence cases were detected at the first screen, they were followed separately and were not part of the randomized comparison. Hence, any effect of X-ray on reducing lung cancer mortality among these cases could not have been determined. It can also be argued that therapeutic advances may render early detection more effective today than at the time of the Mayo trial.

The concern about insufficient size of previous studies of chest X-ray screening is illustrated in Table 2. The uncertainty in interpretation of results from completed studies has led to differences of opinion regarding the value of the annual chest X-ray. Whether a small but important benefit exists can be demonstrated only by a properly designed randomized trial.

Colorectal Cancer Screening

DRE, sigmoidoscopy, and fecal occult blood testing have each been suggested for colorectal cancer screening. However, only the fecal occult blood test has been proven to be beneficial.

Several uncontrolled studies suggesting that the fecal occult blood test leads to early detection have been reported [78–80] as have two case-control studies of the effect of occult blood testing on colorectal cancer mortality. In one study, the screening histories of fatal colorectal cancer cases and matched controls were compared, resulting in an odds ratio of 0.69 for exposure to at least one occult blood test over a 5-year period. The wide confidence interval (0.52–0.91) suggested a benefit from the screening but also the need for further data [81]. In the second study, cases were less likely to have ever been screened than controls. The odds ratio was 0.7 with a 95% confidence interval of 0.5–1.0, consistent with a screening benefit [82].

Five prospective, controlled studies of fecal occult blood testing have also been conducted. The Strang Clinic of New York undertook a nonrandomized study involving some 12,000 screenees and 7000 controls designed to test the effect of combining the stool guaiac test with annual sigmoidoscopy. Individuals were allocated to the study arms by calendar periods. A reduction in colorectal cancer mortality of borderline significance was reported [83].

A randomized trial of the stool guaiac test began in 1974 at the University of Minnesota, where nearly 47,000 persons ages 50–80 were randomized into three groups: a control group, an annually screened group, and a biennially

screened group. The preponderance of test slides were rehydrated. Recent results provided the first definitive evidence that annual testing for occult blood in the stool can reduce the death rate from colorectal cancer. The 13-year cumulative mortality from colorectal cancer was reduced by 33% (mortality ratio 0.67 with 95% confidence interval 0.50–0.87) [84].

A controlled trial in Nottingham, United Kingdom randomized approximately 76,000 individuals to each of two arms using lists of family practitioners. Fecal occult blood testing every 2 years using nonrehydrated slides was offered to the screened arm for three to six rounds of screening. A 15% reduction in colorectal cancer mortality was reported after a median follow-up time of 7.8 years [85].

Two additional randomized trials of occult blood screening were initiated more recently. A trial in Sweden targeted individuals in the narrow age range of 60–64 years [86]. A Danish trial randomized about 31,000 individuals ages 45–75 into two arms. Participants in the screened arm were offered nonrehydrated fecal occult blood tests every 2 years for five rounds over a 10-year period [87, 88]. This trial demonstrated an 18% reduction in colorectal cancer mortality [89].

In summary, testing for occult blood in the stool as a colorectal cancer screening maneuver has been studied in several trials, and a mortality reduction has been demonstrated. The focus of the PLCO trial is therefore flexible sigmoidoscopy.

DRE and rigid sigmoidoscopy were both part of the multiphasic screening program carried out by the Kaiser-Permanente Foundation, and some considered the results of this study to be evidence of the effectiveness of these tests [90]. Approximately 5000 individuals were allocated to a study group urged to receive an annual multiphasic checkup, and a comparable number served as controls. After 11 years, the screened group experienced a colorectal cancer death rate of 1.0 per 1000 participants entered compared to a rate of 3.3 per 1000 in the control group [58, 59]. The observed decrease in colorectal cancer mortality in this study could be a real effect resulting from screening. However, this conclusion has been questioned for several reasons [91]. Some cancers were detected in an investigation of anemia resulting from the multiphasic examination as well as by the two tests. Further, in a reanalysis the investigators found that rates of sigmoidoscopy were low in both groups (control: 25%; screened: 30%), that there was only a slight excess of exposure to sigmoidoscopy in the study group compared to the control group, and that there was not an appreciable difference in removal of colorectal polyps between groups. They concluded that this study should not be used as evidence either for or against sigmoidoscopy screening [92]. DRE made a minor contribution. In addition, a case-control study found no statistically significant mortality reduction from distal rectal cancer using DRE [93].

Two additional observational cohort studies of sigmoidoscopy have been reported. One involved 21,000 participants in Minnesota who underwent an annual physical examination that included sigmoidoscopy [94, 95]. Polyps discovered during screening were removed, and the number of sigmoid cancers ultimately found was only 15% of the number expected. All of the 13 cancers found were localized, and none of the patients had died as of 1979. The second study followed 26,000 men and women in New York [96]. In 50 cancer patients

identified by screening and followed over 15 years, the 5-year survival rate was reported to be 90%. The interpretation that screening was of benefit in these two studies can be questioned on several grounds. Both studies are likely to be affected by self-selection bias of participants and by exclusion of certain individuals from the follow-up process. In the New York study, seven people with a history of symptoms and eight with previously diagnosed lesions were excluded, thereby lowering the observed incidence and mortality rates. In the Minnesota study, cases found at the initial examination were excluded from the observed incidence, and only individuals without gastrointestinal symptoms were allowed to participate. Thus, the data cannot be validly compared with the general population [91]. In addition, the reported survival data from both studies are affected by lead-time and length biases, but no adjustment for these biases was attempted.

Flexible sigmoidoscopy has been shown to be more acceptable to screenees than rigid endoscopy, and the test appears to be very sensitive and highly specific for cancer [97, 98]. The test can discover a high proportion of polyps, and evidence suggests that removal of adenomas decreases the risk of colorectal cancer [99]. The need to address the impact of flexible sigmoidoscopy screening on colorectal cancer mortality has been discussed by several investigators [97, 100, 101]. Encouraging reports of the potential impact of this test come from two case-control studies and from the modeling work of Eddy et al. [102, 103], which suggests a potential mortality reduction of 25–40%. Both case-control studies were conducted in prepaid health plans and used colorectal cancer deaths as cases, with matched controls. Exposure to sigmoidoscopy in cases and controls was compared [104, 105]. Rigid sigmoidoscopy was used in one study, while a majority of the screening was by flexible sigmoidoscopy in the other study. Both studies suggested a strong effect of sigmoidoscopy in reducing colorectal cancer mortality, with unadjusted odds ratios of 0.30 and 0.21. The modeling conclusions and the case-control studies are subject to the assumptions and biases in the methodologies, so that conclusive results will only be obtained from a randomized trial.

Ovarian Cancer Screening

Traditionally, the pelvic examination has been relied on to detect ovarian cancer, but it is insensitive to early disease and small tumors [106]. Thus, most ovarian cancers present as late-stage disease. Two new technologies may be useful as screening tools: CA125 and TVU.

CA125 is an antigenic determinant on a high molecular weight glycoprotein recognized by a monoclonal antibody (OC 125) using an ovarian cell line as an immunogen. The test is performed on peripheral blood. In mostly small (50–150 patients) preoperative studies of women with ovarian masses, serum CA125 levels were elevated (typically above 35 U/mL) in 68–100% of cases averaged over all stages and in 40–50% of stage I disease. Serum CA125 may also be elevated with pregnancy, endometriosis, menstruation, benign ovarian tumors, and with breast, colon, pancreatic, lung, gastric, and liver cancers [107]. CA125 was reported to have high specificity in postmenopausal women in two prospective trials. Among 1010 postmenopausal women undergoing both pelvic examination and CA125, the only malignancy diagnosed was detected

by CA125 [107]. The specificity was 94.3%. In a study in Sweden among 5550 women over 40 years of age, nine cancers were detected, six of the nine by CA125 [108]. Specificity was 98.5% using a threshold of 35 U/mL in women 50 years of age and older. The sensitivity of CA125 was estimated in two nested case-control studies using sera available from two serum banks [109, 110]. The sensitivity for a level of at least 35 U/mL ranged from 20–57% for cases occurring within the first 3 years of follow-up. These two studies also reported a specificity of 95%.

These preoperative and prospective studies together suggest early detection potential for CA125. However, no studies have been conducted to measure sensitivity and specificity in a large screened population, and no randomized trials have been initiated to assess the impact of screening with CA125 on ovarian cancer mortality.

TVU has been proposed for ovarian cancer screening [111], but experience with this modality is limited. In a series of 1017 tumors, 0.3% of ovarian tumors unilocular on ultrasound were malignant, while 8% of those that were multilocular and 39% of those that were solid were malignant [106]. Higgins et al. and Van Nagell et al. [111, 112] have been using TVU for screening women over the age of 40 since 1987. Using 8 cm^3 as the upper limit of normal ovarian volume, 31 abnormal ultrasonograms (in 1000 women) were obtained; 24 of these women underwent laparotomy. TVU identified all three of the cancers detected.

Estimates of yield and false positivity of ultrasound are available from several studies of women offered periodic screening. In a cohort of 801 women ages 40–70 who had one or more risk factors for ovarian cancer, 163 had an abnormal abdominal ultrasound. Surgery was performed in 30 cases, and one borderline ovarian tumor was found [113]. In another study of abdominal ultrasound, 5479 asymptomatic women underwent periodic screening. Of 326 participants who had a positive test and went on to surgery, five women were diagnosed with stage IA or IB ovarian cancer, and four were diagnosed with metastatic ovarian cancer [114]. TVU was also used in a study of 3220 asymptomatic, postmenopausal women. An abnormal exam led to exploratory laparotomy in 44 women. Three primary ovarian carcinomas were found, two with stage IA cancer [115]. Finally, both transvaginal and transabdominal ultrasound were used to screen 1601 women with a first- or second-degree relative who had ovarian cancer. There were 61 positive tests, leading to six ovarian cancers, five stage I. There were five additional cancers, three ovarian and two peritoneal, reported 2–44 months after the last test [116].

The available evidence is not sufficient to determine if the sensitivity and specificity of any single ovarian cancer screening test is adequate for routine application. The modalities may be complementary when used together. The cost of a test such as TVU, as well as the risks and costs associated with surgical evaluation of any positive test result, are potential impediments to general screening. Prospective screening trials to evaluate these modalities are required.

Literature Review

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