

Original Article



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Ovarian cancer screening in menopausal females with a family history of breast or ovarian cancer

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ABSTRACT

Objective: To determine whether annual screening reduces ovarian cancer mortality in women with a family history of breast or ovarian cancer.

Methods: Data was obtained from the Prostate, Lung, Colorectal, and Ovarian cancer trial, a randomized multi-center trial conducted to determine if screening could reduce mortality in these cancers. The trial enrolled 78,216 women, randomized into either a screening arm with annual serum cancer antigen 125 and pelvic ultrasounds, or usual care arm. This study identified a subgroup that reported a first degree relative with breast or ovarian cancer. Analysis was performed to compare overall mortality and disease specific mortality in the screening versus usual care arm. In patients diagnosed with ovarian cancer, stage distribution, and survival were analyzed as a secondary endpoint.

Results: There was no significant difference in overall mortality or disease specific mortality between the two arms. Ovarian cancer was diagnosed in 48 patients in the screening arm and 44 patients in the usual care arm. Screened patients were more likely to be diagnosed at an earlier stage than usual care patients. Patients in the screening arm diagnosed with ovarian cancer experienced a significantly improved survival compared to patients in the usual care arm; relative risk 0.66 (95% CI, 0.47 to 0.93).

Conclusion: Screening did not appear to decrease ovarian cancer mortality in participants with a family history of breast or ovarian cancer. Secondary endpoints, however, showed notable differences. Significantly fewer patients were diagnosed with advanced stage disease in the screening arm; and survival was significantly improved. Further investigation is warranted to assess screening efficacy in women at increased risk.

Keywords: CA-125 Antigen; Mass Screening; Ovarian Neoplasms

INTRODUCTION

Over 20,000 women in the United States are diagnosed with ovarian cancer each year. Most are diagnosed at an advanced stage; early detection remains a challenge. Women with a family history of breast or ovarian cancer are known to be at higher risk for developing

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ovarian cancer. It is unclear; however, whether screening these higher risk patients effectively reduces mortality. Some experts recommend annual screening in the setting of a family history of ovarian or breast cancer [1,2]. Evidence demonstrating a reduction in ovarian cancer mortality, however, is lacking. Guidelines from the United States Preventive Services Task Force (USPSTF) state “Although available evidence does not show with absolute certainty whether the balance of benefits and harms of ovarian cancer screening may differ for women with a family history of ovarian cancer, the USPSTF found no reason to believe that such women would necessarily benefit” [3]. The current study was undertaken to assess the effect of screening on ovarian cancer mortality in this population.

The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening trial was a large prospective trial conducted by the National Cancer Institute (NCI) to determine if screening could decrease mortality for these four index cancers. Over 78,000 healthy menopausal female volunteers were enrolled and randomized to a screening arm and a usual medical care arm. Women in the usual medical care arm continued to receive annual exams, but did not undergo specific screening intervention. Women in the screening arm underwent annual screening for ovarian cancer with pelvic ultrasound and serum cancer antigen 125 (CA-125) levels. The trial results, published in 2011, did not demonstrate any benefit to ovarian cancer screening in this population of average risk patients [4]. The current study utilizes data from the PLCO study to examine ovarian cancer in a subgroup of patients with a family history of breast or ovarian cancer.

MATERIALS AND METHODS

Enrollment for the PLCO trial occurred between November 1993 and July 2001. Institutional Review Boards at the NCI and each screening center approved the study. Women eligible for participation were ages 55 to 74 with no previous diagnosis of lung, colorectal, or ovarian cancer. A total of 78,216 participants were enrolled, and randomized to either a screening arm or a usual medical care arm. All participants completed a detailed baseline questionnaire, which included information on personal and family medical history. In the screening arm, participants underwent a baseline pelvic ultrasound and serum CA-125, with subsequent annual pelvic ultrasound for an additional 3 years, and annual CA-125 for 5 years. Abnormal screening was determined by a CA-125 greater than 35 U/mL, or any of the following abnormalities on pelvic ultrasound: ovarian volume greater than 10 mL, cyst volume greater than 10 mL, any solid area of papillary projection, or any cyst with mixed components. The usual care group did not undergo cancer specific screening.

The participants and physicians were notified of abnormal screening results; diagnostic and therapeutic interventions were at the discretion of the primary physician. Follow-up data was obtained from review of the medical record, annual questionnaires, population-based cancer registries, and death certificates. Participants were followed for a minimum of 10 years. Detailed information regarding the PLCO methodology has been published in previous publications from the PLCO group [4-10].

The current study defined a subgroup of participants who reported at least one first degree relative with breast cancer or at least one first degree relative with ovarian cancer. There were 22,355 participants (28.6% of enrollees) identified for inclusion in this subgroup analysis.

A separate subgroup of patients with a personal history of breast cancer prior to enrollment was also analyzed. There were 2,708 participants (3.5% of enrollees) identified for inclusion in this subgroup. The current study compared overall mortality and disease specific mortality between the screened group and the usual care group. For patients diagnosed with ovarian cancer, stage at diagnosis and survival were analyzed as endpoints.

Chi-square tests were used to compare the mortality rate between the screening arm and the usual care (control) arm. Relative risk (RR) for the screening group and the 95% CI were estimated by comparing the mortality rate for the screening group with that of the control group. Survival between the screening and control group were compared with Cox proportional hazard regression tests. To minimize the impact of lead time bias, survival was calculated from the date of enrollment to date of exit or death. The data analysis was generated using SAS ver. 9.3 software (SAS Institute Inc., Cary, NC, USA). Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. A two-tailed p-value of less than 0.05 was regarded as statistically significant.

RESULTS

In the original PLCO trial there were 39,105 subjects randomized to annual screening; 212 women were diagnosed with ovarian cancer, and 118 women died from ovarian cancer. There were 39,111 women randomized to the usual care group; 176 women developed ovarian cancer, and there were 100 deaths due to ovarian cancer [4]. In the current study there were 11,293 subjects in the screening group that reported at least one first degree relative with breast or ovarian cancer, and 11,062 subjects in the usual care group. Patient characteristics are described in **Table 1**. An additional subgroup of subjects that reported a personal history of breast cancer was also studied. There was no difference in overall mortality or ovarian cancer mortality between the screened population and the usual care population. For women with a family history of breast or ovarian cancer, the RR for overall mortality in the screened group versus usual care group was RR=0.99 (95% CI, 0.93 to 1.06). The RR for ovarian cancer mortality in the screened group versus usual care group was RR=0.66 (95% CI, 0.39 to 1.12).

There were 48 subjects in the screened group with a positive family history that were diagnosed with ovarian cancer. There were 44 subjects in the usual care group diagnosed

Table 1. Characteristics of women with a family history of breast/ovarian cancer in the screening (n=11,293) versus usual care group (n=11,062)

Characteristic	Screening group (n=11,293)	Usual care group (n=11,062)	p-value
Mean age (yr)	62.8±5.4	62.9±5.5	0.26
Race			0.85
White, non-hispanic	10,239 (90.7)	10,022 (90.6)	
Black, non-hispanic	464 (4.1)	471 (4.3)	
Hispanic	170 (1.5)	176 (1.6)	
Asian	322 (2.9)	315 (2.9)	
Pacific Islander	63 (0.6)	53 (0.48)	
American Indian	32 (0.3)	23 (0.21)	
Missing	3 (<0.1)	2 (<0.1)	
Family history of ≥2 first degree relatives with breast/ovarian cancer	918 (8.1)	912 (8.2)	0.76
Family history of breast/ovarian cancer diagnosed <50 years	3,520 (31.2)	3,426 (31.0)	0.75
Patients diagnosed with ovarian cancer	48 (0.4)	44 (0.4)	0.75

Values are presented as mean±SD or number (%).

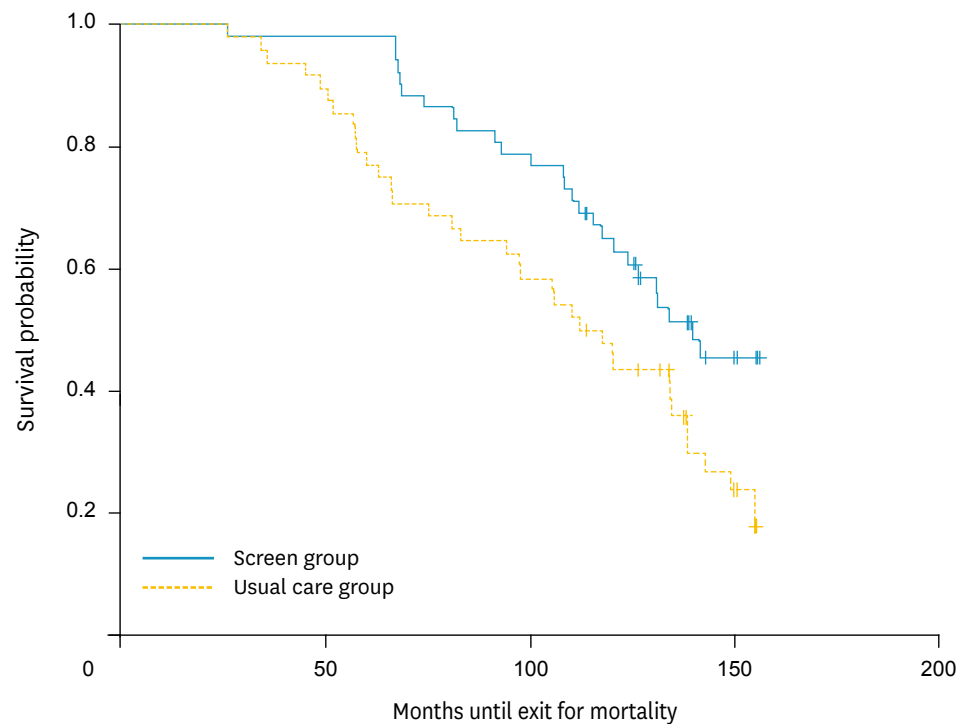


Fig. 1. Survival curves in patients diagnosed with ovarian cancer in the screened versus usual care group.

with ovarian cancer. There was no significant difference between these two groups with regard to age, tumor grade, or histology (serous versus non-serous tumors). For patients diagnosed with ovarian cancer, there were 23 that died in the screened group versus 32 that died in the usual care group. Survival in patients with ovarian cancer was improved in the screened group versus the usual care group, RR=0.66 (95% CI, 0.47 to 0.93). Survival curves for patients with a positive family history are demonstrated in Fig. 1. Survival was calculated from the time of enrollment, not diagnosis, and was significantly improved in the screening group. However, this apparent improvement in survival did not translate into reduced ovarian cancer mortality.

Patients with a personal history of breast cancer prior to enrollment were examined as a separate subgroup. This was a relatively small group, with 1,351 patients in the screening arm and 1,357 in the usual care arm. There were six patients diagnosed with ovarian cancer in the screening arm and five in the usual care arm. There were three deaths due to ovarian cancer in the screening arm and four in the usual care arm. The small number of events in this group precluded an assessment of the efficacy of screening.

Stage at diagnosis was analyzed to determine if screening was associated with a higher proportion of early stage cancer. For patients with a family history of breast and/or ovarian cancer there was a trend towards diagnosis in stage I or II, 29% stage I or II in the screened group versus 17% stage I or II in the usual care group ($p=0.085$). A separate analysis was performed to assess if screening resulted in a significant stage shift in patients potentially in the presymptomatic phase. When stages I, II, IIIA, and IIIB were compared to stage IIIC and IV, the screening group had a statistically significant decrease in stage IIIC and IV at presentation compared to the usual care group (52% stage IIIC and IV for screening, 75%

for usual care, $p=0.031$). These results indicate a trend towards earlier stage associated with screening, and a significant reduction in advanced bulky disease at diagnosis.

DISCUSSION

Screening for ovarian cancer in the general population is generally not considered effective. Screening for women at higher risk, however, remains controversial. Stirling et al. [11] reported that annual screening with transvaginal ultrasound and CA-125 levels did not reduce ovarian cancer mortality in a cohort of 1,110 high risk women. In a cohort of 312 BRCA mutation carriers and members of hereditary breast and ovarian cancer families, Olivier et al. [12] also were not able to demonstrate a reduction in mortality through screening. The current study examines over 22,000 patients enrolled in the PLCO trial with a positive family history; screening with ultrasound and CA-125 did not reduce ovarian cancer mortality.

Trials investigating screening efficacy must demonstrate a reduction in site-specific mortality in the screening arm, compared to the control arm. Secondary endpoints, however, may be useful, and may be indicative of a potential benefit to screening [13]. A down-staging of screen detected tumors, stage shift, is necessary for screening to be effective for ovarian cancer. The concern, however, is that increased detection of early stage tumors may not necessarily decrease cancer mortality; particularly if it is not associated with an absolute reduction in advanced stage cancers [14]. This phenomenon, increased detection of non-lethal subclinical malignancies through screening, is termed length-biased sampling. In the current study, the increase in early stage cancers is associated with a significant reduction in the absolute number of stage IIIC and IV cancers. Cancers in the screened group were similar to cancers in the control group with regard to histology and grade. These observations suggest a direct correlation between stage shift and survival, rather than a bias effect.

Women with a first degree relative with breast or ovarian cancer are at substantially higher risk of developing ovarian cancer. With a family history of ovarian cancer, the RR is 3.1 [15]; and with a family history of breast cancer, the RR is 1.4 [16]. However, the current study did not find a higher incidence of ovarian cancer in patients with a positive family history compared to patients with a negative family history. Approximately 19% of women with ovarian cancer and a first degree relative with breast or ovarian cancer carry a deleterious BRCA mutation [17]. Breast and ovarian cancer may be associated with other lower penetrance gene mutations in up to 11% of patients [18]. The PLCO study started enrolling patients in 1993. BRCA testing, therefore, was costly and not widely available during the time period of this trial; it can be assumed that the majority of patients in this trial did not undergo genetic evaluation. In the absence of genetic testing, it is difficult to quantitate the level of cancer risk for this population. Therefore the study population represents a heterogeneous group of patients, some with and some without genetic mutations. As a whole, this may be construed as an intermediate or moderate risk group. Nonetheless, this was seen as a clinically useful approach, as many patients with a positive family history will inquire about screening but may not have the resources or desire to undergo genetic evaluation.

Additional considerations suggest that screening might be effective in the positive family history subgroup. The biology of hereditary tumors may be inherently different than sporadic ovarian cancer. Hereditary tumors appear to be associated with a better prognosis [19],

suggesting that a modest improvement in early diagnosis may translate into a significant improvement in outcome. While the current study did not demonstrate a decrease in mortality in the screening group, a significant improvement in survival was noted in those diagnosed with ovarian cancer. When assessing survival, it is difficult to eliminate the impact of lead-time bias. Detection of a cancer at an earlier stage may appear to improve survival by advancing the time of diagnosis. To adjust for lead-time bias, the current study analyzed survival from the time of enrollment to a fixed follow-up time point. A statistically significant improvement in survival was observed in the screening arm. Despite the improvement in survival in this group, a statistically significant improvement in overall and disease specific mortality was not observed. This study also demonstrated a significant stage shift, suggesting that the inability to detect a difference in mortality may be due to the small numbers included in this analysis. Although caution is necessary in interpreting these secondary endpoints, the results indicate a potential benefit to screening individuals with a positive family history.

Patients with a personal history of breast cancer were examined as a separate subgroup. Given the small number of events in this group, it was not possible to determine whether patients with a personal history of breast cancer would benefit from annual screening. Intuitively, however, one suspects this constitutes a higher risk group. When this group is included with the positive family history group, survival results remain statistically significant. Therefore, patients with a personal history of breast cancer may benefit from the same screening approach as those with a positive family history.

Currently, there are two ongoing prospective trials underway to assess the utility of screening for ovarian cancer in high risk women: The United Kingdom Familial Ovarian Cancer Screening Study (UK FOCSS), and the Gynecologic Oncology Group (GOG) Trial 199. Unlike the current study, these two trials have the ability to risk stratify the study populations based on both family history and BRCA status. Participants declining risk reducing salpingo-oophorectomy were offered screening. Preliminary results of the UK FOCSS study were published in 2012 [20]. This trial includes patients that are known BRCA positive and/or estimated to have an ovarian cancer lifetime risk of at least 10%. Almost all cancers identified in this preliminary report occurred in women with known genetic mutations. Only four cancers were identified among the 2,960 participants without a known mutation (0.14%), compared to 30 cancers among the 538 BRCA mutation carriers (5.6%). This finding prompted an editorial, suggesting that family history alone is not sufficient to assess ovarian cancer risk, and genetic testing should be included in screening trials of high risk women [21].

The GOG trial utilizes the Risk of Ovarian Cancer Algorithm, a longitudinal screening strategy designed to be more effective than annual screening [22]. This trial includes BRCA testing in the research environment, with disclosure to the patient on request. Results of this trial are expected soon.

In conclusion, data from the PLCO trial indicates that screening women who have a family history of breast or ovarian cancer does not reduce ovarian cancer mortality. Similarly, results of the original PLCO trial, for average risk women, did not demonstrate a reduction in ovarian cancer mortality associated with screening. There was also no evidence of stage shift, or improvement in survival for the average risk population. The current study, however, noted significant differences in the number of patients presenting with advanced bulky disease, and in survival in those diagnosed with ovarian cancer. Although inherent issues such as

length-bias sampling and lead-time bias cannot be entirely excluded, these results suggest that patients with a positive family history represent a distinct subgroup. Studies currently underway are anticipated to provide additional guidance.

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