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Extended Mortality Results for Ovarian Cancer Screening in the PLCO Trial with Median 15 Years Follow-up

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Abstract

Background—The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial originally reported no mortality benefit of ovarian cancer screening after a median of 12.4 years of follow-up. The UKCTOCS screening trial failed to show a statistically significant mortality reduction in the primary analysis but reported an apparent increased mortality benefit in trial years 7–14 compared to 0–7. Here we report an updated analysis of PLCO with extended mortality follow-up.

Methods—Participants were randomized from 1993–2001 at ten U.S. centers to an intervention or usual care arm. Intervention arm women were screened for ovarian cancer with annual transvaginal ultrasound (TVU) (4 years) and CA-125 (6 years), with a fixed cutoff at 35 U/ml for CA-125. The original follow-up period was for up to 13 years (median follow-up 12.4 years); in this analysis follow-up for mortality was extended by up to 6 years.

Results—39105 (intervention) and 39111 (usual care) women were randomized, of which 34253 and 34304, respectively, had at least one ovary at baseline. Median follow-up was 14.7 years in each arm and maximum follow-up 19.2 years in each arm. A total of 187 (intervention) and 176 (usual care) deaths from ovarian cancer were observed, for a risk-ratio of 1.06 (95% CI: 0.87–1.30). Risk-ratios were similar for study years 0–7 (RR=1.04), 7–14 (RR=1.06) and 14+ (RR=1.09). The risk ratio for all-cause mortality was 1.01 (95% CI: 0.97–1.05). Ovarian cancer specific survival was not significantly different across trial arms (p=0.16).

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Conflict of Interest Statement

The authors report no conflicts of interest.

Conclusion—Extended follow-up of PLCO indicated no mortality benefit from screening for ovarian cancer with CA-125 and TVU.

Introduction

Ovarian cancer is the fifth leading cause of cancer deaths in U.S. women, with approximately 14,000 reported annually¹. Due to its usual presentation in late stages and high case-fatality rate when detected late, there has been a strong research interest in screening for ovarian cancer over the last several decades. In 2011, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial reported its results of screening with the biomarker CA-125 along with transvaginal ultrasound (TVU)². There was no demonstrated mortality benefit of screening after a median follow-up of 12.4 years (range 10.9 to 13.0 years), with a reported ovarian cancer mortality risk ratio (RR) of 1.18 (95% CI: 0.82–1.71). In addition, various harms of screening were reported, including oophorectomies for benign disease.

In 2015, another large ovarian cancer screening trial, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), reported its findings³. UKCTOCS was designed with a control arm and two screening arms. One screening arm employed TVU alone while the other employed a multi-modal screening paradigm (MMS) that utilized longitudinal CA-125 values quantified by the Risk of Ovarian Cancer (ROCA) algorithm as the initial screen, with subsequent triaging to repeat CA-125 or TVU. Based on the primary endpoint of ovarian cancer specific mortality, neither screening arm demonstrated a statistically significant reduction compared to the control arm, with reductions of 15% (95% CI: –3 to 30) and 11% (95% CI: –7 to 27) for the MMS and TVU arms, respectively.

Although the primary endpoint did not reach statistical significance, the cumulative ovarian mortality curves in UKCTOCS for the screening arms as compared to the control arm began to separate around 10 to 12 years from randomization and reached greatest separation at 14 years, the maximum follow-up time in the trial. In a data-driven post-hoc analysis, the reported mortality reductions for MMS compared to control were 8% (95% CI: –20 to 31) for the first 7 years of the trial versus 23% (95% CI: 1–46) for years 7–14. Until longer term follow-up is reported, it is not known whether any trend toward increasing separation of the mortality curves will continue (or increase) beyond 14 years.

In this analysis, we therefore present updated PLCO mortality data for an additional three to six years, extending the total period of follow-up for PLCO to 13 to 19 years from randomization. This covers, and extends, the period for which the mortality curves were beginning to show maximum separation in UKCTOCS. The results of this analysis will show whether a similar phenomenon at a similar trial time-point was observed in PLCO. Further, with more ovarian cancer deaths, these results will give a more precise estimate of any mortality benefit of ovarian cancer screening as practiced in PLCO.

Methods

The design and methods of the PLCO Trial have been described^{2,4}. Briefly, randomization at ten U.S. screening centers to either an intervention or usual care arm occurred from 1993–

2001. Women were considered eligible if they were ages 55–74 and had no previous diagnosis of lung, colorectal or ovarian cancer. Two initial PLCO exclusion criteria – previous oophorectomy and current tamoxifen use – were dropped in 1996 and 1999, respectively. Women with prior bilateral oophorectomy were screened for lung and colorectal cancer but not ovarian cancer. At study entry, participants completed a self-administered baseline questionnaire that included demographics, general risk factors, and screening and medical histories. The trial was approved by each institution's Institutional Review Board and all participants provided informed consent. The trial was registered at clinicaltrials.gov (NCT00002540).

Screening Examinations

Women in the intervention arm received a CA-125 blood test and TVU at baseline, an annual TVU for three more years and an annual CA-125 for five more years. Bimanual examination of the ovaries, originally part of the screening procedures, was dropped from the study protocol in December 1998 because no cancers were detected solely by ovarian palpation. Participants also received chest radiographs annually for four years and flexible sigmoidoscopy at baseline and year three or five. CA-125 results ≥ 35 U/mL were classified as abnormal. TVU was conducted by trained examiners using a 5 to 7.5 MHz transvaginal probe, with the following results classified as abnormal: 1) ovarian volume greater than 10 cubic cm; 2) cyst volume greater than 10 cubic cm; 3) any solid area or papillary projection extending into the cavity of a cystic ovarian tumor of any size; and 4) any mixed (solid/cystic) component within a cystic ovarian tumor.

Participants and their physicians were notified in writing of any suspicious abnormality on screening. The diagnostic process following a positive screen was managed by participants' primary care physicians, and was not dictated by the trial.

Ascertainment of Study End-points

The primary trial endpoint for the ovarian component of PLCO was ovarian cancer-specific mortality; secondary endpoints included ovarian cancer incidence, cancer stage, survival, harms of screening, contamination and compliance, and all-cause mortality.

The original analysis period for the PLCO ovarian component was from randomization through 13 years of follow-up or Feb 28th, 2010, whichever came first². Trial endpoints (incident ovarian cancers, ovarian cancer deaths and all-cause deaths) for this period have been described in previous publications. For this original analysis period, incident cancers and deaths were ascertained primarily through a mailed annual study update questionnaire (ASU). Incident cancers reported on the ASU were verified by obtaining medical records and utilizing a standardized abstracting process. Next of kin notified the trial of deaths, which were verified by obtaining death certificates; NDI searches were also used. The underlying cause of death was determined in a uniform and unbiased manner from the death certificate and medical records in a blinded endpoint verification process by an independent death review committee that has been described in detail previously⁵.

Going forward from the time of the original analysis period, there was a structural change in the operation of PLCO that affected the way cancer incidence and mortality endpoints were

ascertained. Specifically, beginning in mid-2011, PLCO transitioned from a system of follow-up performed at the individual screening centers to a centralized approach in which subjects were followed by a central data coordinating center (CDCC). This required re-consent of all PLCO subjects alive at the time of transition. The consenting process offered subjects the following three options: active follow-up, passive follow-up and refusal of further follow-up. Active participants had their personal identifying information (PII) transferred to the CDCC; they were eligible for linkages to NDI and state cancer registries and also could be contracted directly to fill out questionnaires or for future specimen collections. Passive participants did not have their PII transferred but could still be passively followed by their original screening centers through NDI and state cancer registries; those known to be deceased at the time of transfer were considered as passive participants. Finally, refusers had no further active or passive follow-up.

All active and passive subjects were linked to the NDI, with complete death information through the end of 2012. For these subjects, the end-of-follow-up for mortality for this analysis was December 31st, 2012 or date of death, whichever came first. For refusers, since they had to actively refuse and thus were known to be alive at their refusal date (which ranged from mid-2011 until mid-2012 at nine centers and 2014 at one center), their end of follow-up was their refusal date or December 31, 2012, whichever came first.

As in the original analysis, deaths from ovarian, peritoneal and fallopian tube cancers were counted as deaths from ovarian cancer. Also, as in the original analysis, women without at least one ovary at baseline were excluded. In computing all-cause mortality, deaths from lung and colorectal cancer were excluded because trial participants were screened for those cancers and extended mortality follow-up for them is ongoing.

For the extended analysis, the trial ascertained deaths primarily through the NDI, so medical records were not available to perform endpoint verification. Therefore, for deaths occurring after the original cutoff (Feb 28th, 2010), the underlying cause of death from the NDI was used to classify deaths as being from ovarian cancer or not and no endpoint verification was performed; for deaths before that date, the endpoint-verified classifications used in the original report were also used here. Alternative analyses were performed to assess the effect of using only death certificate (or NDI) information instead of the endpoint-verified classifications for the originally reported deaths.

We only report here on mortality outcomes. Linkage with cancer registries to ascertain incident ovarian cancers is ongoing, so complete incidence data for the period after Feb 28th, 2010 are not currently available. However, for those ovarian cancers reported from the original analysis period, 243 in the intervention and 218 in the usual care arm, we analyzed survival based on the updated mortality data⁶.

To ascertain contamination, i.e., use of CA-125 and TVU testing in usual care arm women, annual or biennial surveys were conducted in a 1% random sample of these women ; the surveys continued from baseline through study year 17.

Statistical Methods

Mortality rates from ovarian cancer were defined as deaths from ovarian cancer during the follow-up period divided by the person years (PY) of follow-up. The rate-ratio (RR) of the intervention to usual care arm was computed as the ratio of the rates in the two arms. The 95% confidence interval for the RR was calculated assuming a Poisson distribution of events and using the profile likelihood method⁷. The Kaplan-Meier method was used to analyze ovarian cancer survival by arm and mode of detection⁸.

Results

For the current analysis, there were 34,253 (intervention arm) and 34,304 (usual care arm) women with at least one ovary at baseline; the total numbers randomized were 39,105 (intervention) versus 39,111 (usual care).

The demographics and medical history of subjects were similar across arms (Table 1). A total of 88.5% were non-Hispanic white and 35% were age 65 or over at randomization.

With respect to transfer status to centralized follow-up, the proportion of refusers was slightly higher in the usual care (15.6%) than the intervention arm (12.0%) ($p < 0.001$). The follow-up time for refusers, median 14.5 (intervention) and 14.3 (usual care) years, was slightly shorter than that for active/passive subjects, median 14.8 (intervention) and 14.7 (usual care) years. Overall, follow-up time was essentially equal across arms, with median (25th/75th) time of 14.72 years (13.1/16.4) versus 14.65 years (12.8/15.7) years in the intervention and usual care arms, respectively. The maximum follow-up was 19.2 years in each arm.

As previously reported for the screening years of the trial, 2.3–3.2% of usual care arm women reported having a CA-125 test and 2.7–4.6% reported having a TVU exam in the prior year². In the post-screening period, 1.8% and 2.9% of usual care arm women reported having a CA-125 and TVU exam, respectively, in the prior year; 7.5% (CA-125) and 14.9% (TVU) reported ever having had these tests. Intervention arm compliance with screening per round ranged from 73–85% for CA-125 and 78–84% for TVU. In the post-screening period, 3.2% and 2.6% of intervention arm women reported having a CA-125 and TVU test, respectively, in the prior year, and 7.8% (CA-125) and 11.2% (TVU) reported ever having had these tests outside of the PLCO trial.

Table 2 shows deaths from ovarian cancer by arm. A total of 187 ovarian cancer deaths (rate 38.2 per 100,000 PY) were observed in the intervention versus 176 (rate 36.0 per 100,000 PY) in the usual care arm. The rate ratio (RR) was 1.06 (95% CI: 0.86–1.31). A similar rate ratio (1.08) was observed after excluding primary peritoneal cancers. Figure 1 displays ovarian cancer deaths by study time. By study time period, RRs were similar; 1.04 (95% CI: 0.7–1.5), 1.06 (95% CI: 0.8–1.4) and 1.09 (95% CI: 0.7–1.8) for years 0–7, 7–14 and > 14, respectively. All-cause mortality rates were 1046 and 1035 (per 100,000 PY) in the intervention and usual care arms, respectively, RR=1.01 (95% CI: 0.97–1.05).

As mentioned above, for the newly determined deaths endpoint verification was not performed due to lack of medical records collected. To examine the potential impact of this, we re-performed the analysis using only death certificate or NDI underlying cause data for all deaths. The RR was unchanged at 1.06.

Table 3 shows the distribution of all-cause mortality. The proportions from the various causes of deaths were similar across arms.

Survival

Survival with updated mortality data was examined for the ovarian cancer cases previously reported from the original analysis period, specifically, 243 intervention and 218 usual care arm cases. Of the 243 intervention arm cases, 73 were screen detected (diagnosed within one year of a positive screen), 28 were interval (diagnosed within 1 year of a negative screen), 114 were post-screening (diagnosed more than one year after the last screen) and 28 were never screened.

Figure 2 shows ovarian-cancer specific survival curves (from date of diagnosis) by arm and mode of detection for the previously reported incident cancers, using the updated mortality data. Survival was modestly higher at five years in the intervention as compared to usual care arm (47.4% versus 36.0%) but similar at 10 years (31.3% versus 27.1%); overall, there was no statistically significant survival difference by arm ($p=0.16$, log-rank test). Survival as measured from time of randomization is often used in screening trials to correct for lead time bias when comparing survival across arms; as measured from randomization, survival was similar across arms ($p=0.67$, log-rank test). Within the intervention arm, screen detected cases had borderline significantly improved survival compared to non-screen detected cases ($p=0.04$, log-rank test). Survival was about 15% higher at five years among screen-detected cases (57.8% versus 43.1%) but similar at 12 years (25.1% versus 22.8%). Ovarian cancer deaths from all of these previously reported cases comprised 85% (159 of 187) and 84% (147 of 176) of all ovarian cancer deaths in the intervention and usual care arms, respectively.

Discussion

In this update of the PLCO ovarian cancer screening trial, median follow-up for mortality was extended by 2.3 years (to 14.7 years), maximum follow-up was extended by six years, and ovarian cancer deaths increased by 67%. There was no change in the basic finding of no mortality benefit of screening with CA-125 and TVU, with the rate ratio decreasing slightly toward the null, from 1.18 to 1.06. The relatively tight 95% confidence interval, with a lower limit of 0.86, indicates that it is unlikely that the true mortality benefit of screening with CA-125 and TVU was substantial ($> 15\%$). Extended analysis of survival of previously reported cases showed no significant difference across arms (as measured from either time of diagnosis or time of randomization), and within the intervention arm, only a modest survival difference between screen-detected and non-screen detected cases. Note that since there was no mortality benefit of screening, this small survival advantage of the screen-detected cases was likely due to the well-known biases of lead-time, length-biased sampling

and overdiagnosis. Compliance with screening was high and usual care arm contamination relatively low.

Even if screening for ovarian cancer were clearly shown to produce a mortality benefit, because it is a relatively rare disease, with only about one third as many deaths as breast cancer in the U.S., the questions of cost-effectiveness and benefits to harms ratio loom large. As previously reported in PLCO, the harms of ovarian cancer screening included a large number of oophorectomies performed. Of 3285 (9.6%) intervention arm women with a false positive result during the trial, 32.9% underwent surgery (typically oophorectomy) as part of the diagnostic work-up². One possible method of increasing the benefits to harm ratio of screening, as well as the cost-effectiveness, is using risk-stratification to identify a high-risk population^{9,10}. However, readily available demographic, behavioral and clinical data provide relatively little potential for effective risk stratification in the general population, outside of rare high-risk groups such as known *BRCA1* or *BRCA2* carriers¹¹. An analysis of the population distribution of the lifetime risk of ovarian cancer based on medical history factors (oral contraceptive use, parity, tubal ligation, endometriosis and family history of ovarian cancer) in conjunction with a genetic risk score showed limited risk stratification levels¹². Only 1.85% of the population had a lifetime risk of at least 4.0%, or about 3 times higher than the overall population average; these 1.85% would comprise approximately 6% of all ovarian cancer cases. In such a group the risk of dying from ovarian cancer would be similar to that of dying from breast cancer in the general population. Screening limited to such a group, even if modestly effective, would have little impact on overall ovarian cancer mortality rates. Further, even this level of risk stratification was only achieved incorporating a genetic risk score, which would not generally be available for most women.

As discussed above, in UKCTOCS, although the primary endpoint did not reach statistical significance, there was some evidence of increased mortality reduction in the later trial years (years 7–14)³. To interpret trends of mortality with time on study, however, it is important to consider the timing of the scheduled screening rounds, which differed somewhat between PLCO and UKCTOCS. In PLCO, women generally were scheduled for 6 annual screening rounds whereas women in UKCTOCS underwent screening for 7–11 annual rounds. Therefore, even if screening had the same underlying benefit in both trials, the mortality trajectories over time could differ. Nonetheless, the fact that no benefit was observed in PLCO over the entire period of follow-up of UKCTOCS (through 14 years) and beyond, plus the finding of similar mortality risk ratios during the different time periods of PLCO, suggests strongly that the reason that no mortality reduction was seen in PLCO was not because of inadequate length of follow-up.

A prior analysis retrospectively applying the ROCA algorithm to PLCO screen results, in an effort to replicate the MMS arm of UKCTOCS, showed that even in a best case scenario, having used ROCA in PLCO would not have led to a statistically significant mortality benefit of ovarian cancer screening⁶. There is some evidence that use of a longitudinal algorithm for CA-125 can detect ovarian cancer earlier than using a fixed cutoff as was employed in PLCO¹³. However, although the MMS arm (which employed the longitudinal algorithm ROCA) has often been emphasized with respect to the UKCTOCS findings, it is not clear that any suggested reduction in ovarian cancer mortality was greater in the MMS

than the USS (ultrasound) arm. Again, neither arm showed a statistically significant reduction in ovarian cancer mortality versus the control arm in the primary analysis. In terms of point estimates of the magnitude of mortality reduction, though, the two active arms were quite close in all primary and secondary mortality analyses; all within 4 percentage points, and all within 2 percentage points for the analyses that included primary peritoneal cancer. This finding of a similar observed effect for both active arms makes sense intuitively because in the MMS arm the triage pathway to full clinical assessment generally required having a positive ultrasound at some point, except for women with a repeat ROCA finding of elevated risk, which was a minority of all women referred for further testing (by design in the MMS arm 15% of all women screened were classified as intermediate risk and 2% as elevated risk). In PLCO, for 4 of the 6 screening rounds, all women received an ultrasound (TVU) at the screen and a positive finding on ultrasound was considered a positive screen requiring further work-up, regardless of the CA-125 level.

Conclusion

Extended follow-up of the PLCO trial through up to 19 years continues to indicate no mortality benefit of screening with CA-125 and TVU.

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Highlights

After median follow-up of 15 years, screening with CA-125 and transvaginal ultrasound did not reduce ovarian cancer mortality

Ovarian cancer mortality rates were 38.2 (screened arm) versus 36.0 (control arm) per 100,000 person-years; risk ratio was 1.06(95% CI:0.87–1.30).

Ovarian cancer survival was not significantly different by trial arm, with similar survival rates at 10 years

Figure 1. Deaths from ovarian cancer by arm and years from randomization. Red (solid) line is intervention arm, black (dotted) line is usual care arm. Numbers still at risk at selected time points are listed below the graph.

a

b

Figure 2.

A) Ovarian cancer-specific survival by arm. Red (solid) line is intervention arm, black (dotted) line is usual care arm. B) Ovarian cancer-specific survival by mode of detection in the intervention arm. Red (solid) line is for screen detected cases, black (dotted) line is for non-screen detected cases. P-values (log-rank test) for difference in survival between arms and between screen detected and non-screen detected cases were 0.16 and 0.04, respectively.

Table 1

Demographics and medical history of PLCO population

		Intervention (N=34253)	Usual Care (N=34304)
Age	55–59	11698 (34.2)	11728 (34.2)
	60–64	10405 (30.4)	10398 (30.3)
	65–69	7497 (21.9)	7506 (21.9)
	70–74	4653 (13.6)	4672 (13.6)
Race/Ethnicity	Non-Hispanic White	29502 (88.6)	29292 (88.4)
	Non-Hispanic Black	1896 (5.7)	1897 (5.7)
	Hispanic	512 (1.5)	512 (1.5)
	Asian	1138 (3.4)	1190 (3.6)
	Am Indian/Alaska Native	250 (0.8)	253 (0.8)
Education	Less than High School	2175 (6.6)	2142 (6.5)
	High School	13308 (40.0)	13308 (40.5)
	Some College	7688 (23.1)	7483 (22.7)
	College Graduate	5156 (15.5)	4999 (15.1)
	Post-graduate Study	4926 (14.8)	5020 (15.1)
Prior Hysterectomy		9083 (27.3)	8979 (27.2)
Prior Oral Contraceptive Use		17822 (53.6)	17883 (54.1)
Prior Hormone Therapy Use		20992 (63.4)	20744 (63.0)
Personal History of Breast Cancer		1200 (3.6)	1186 (3.6)
Family History of Breast or Ovarian Cancer		5592 (17.6)	5437 (17.3)

Note: Percentages exclude unknowns except for age. Unknown percentage was less than or equal to 5% for each factor in each arm.

Table 2

Ovarian cancer and all-cause mortality by arm

	Intervention	Usual Care	RR (95% CI)
Person Years (PY)	490109	489253	
Cause of Death	N (rate per 100000 PY)	N (rate per 100000 PY)	
Ovarian Cancer ¹	187 (38.2)	176 (36.0)	1.06 (0.87,1.30)
Ovarian cancer (excluding primary peritoneal cancer) ²	181 (36.9)	168 (34.3)	1.08 (0.87,1.33)
All-cause ³	5135 (1047.7)	5077 (1037.7)	1.01 (0.972,1.051)

¹Includes fallopian tube and primary peritoneal cancer²Includes fallopian tube cancer³Excluding colorectal cancer and lung cancer

Table 3

Causes of death by arm

	Intervention	Usual Care
Cause of Death	N(%)	N(%)
Ovarian Cancer	187 (3.6)	176 (3.5)
Other Cancer (excluding lung & colorectal)	1178 (23.0)	1167 (23.0)
Ischemic Heart Disease	580 (11.3)	597 (11.8)
Cerebrovascular Accident	371 (7.2)	376 (7.4)
Other Circulatory Disease	701 (13.7)	718 (14.2)
Respiratory Disease	570 (11.1)	523 (10.3)
Digestive Disease	186 (3.6)	162 (3.2)
Infectious Disease	122 (2.4)	110 (2.2)
Endocrine & Metabolic	212 (4.1)	174 (3.4)
Nervous System	306 (6.0)	270 (5.3)
Accidental	197 (3.8)	210 (4.2)
Other	525 (10.2)	594 (11.7)
Total (excluding lung & colorectal)	5135	5077