Commentary

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Ovarian cancer screening effectiveness: A realization from the UK Collaborative Trial of Ovarian Cancer Screening

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Abstract

Effects on survival in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was reported in *The Lancet*, and demonstrate that reductions in disease-specific mortality in this randomized control trial (RCT) indicate that ovarian cancer screening works. The UKCTOCS was large enough for sufficient accrual and follow-up, using two intervention arms: MMS (a multimodal strategy using the biomarker Ca125 combined with ultrasound as a secondary test) and USS (ultrasound alone) compared against a no-screen control group. MMS and USS performed similarly, showing a statistically significant reduction in mortality that increased with follow-up surveillance (8% reduction in years 0–7 vs 28% in years 7–14). The data led to the estimate that 641 screens are needed to prevent one ovarian cancer death.

Keywords

efficacy, mortality reduction, ovarian cancer screening, potential for effectiveness, ultrasound

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In mid-December 2015, the long anticipated effect on survival in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was reported online in *The Lancet* and was followed by the print version in March 2016.[1] My view in this commentary is that reductions in disease-specific mortality of incident cases in this randomized controlled trial (RCT) formulate a strong statement that ovarian cancer screening works. In addition, I present here my commentary on some of the comments already published by others.

The newly reported aspects in the *Lancet* paper[1] that are strikingly significant are as follows:

1. Examination of screening for incident cancers;
2. Mortality reduction in the women screened for incident cancers;
3. Rigorous examination of the results, including application of analytics utilized by investigators with different and opposite findings.[2]

The strength of the UKCTOCS is that it contained an unscreened control arm that was accrued concomitant with the screening arms so that survival between these arms reflected presumed equivalency in the groups under comparison with the only difference considered to be screening versus no screening. Prior to the *Lancet* paper,[1] the status of ovarian cancer screening was that three of four trials found successful detection of highly curable early-stage disease,[3–5] while one trial failed to detect early-stage disease or find any survival benefit because ovarian cancer deaths in the screened and unscreened arms were statistically similar.[2] This RCT known as the PLCO trial[2] (The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial) was conducted in the United States and it published failure to detect early-stage disease and failure to demonstrate survival benefits. Publication of the PLCO results led to reports in the media that screening does more harm than good and embellished the terminology of over-diagnosis due to the high percentage of women without a malignancy that were advanced to surgery in the PLCO trial (1 malignancy in every 19 surgeries).[6] Shortly thereafter, the US Preventive Services Task Force issued a view that recommended against ovarian cancer screening and a "D" grade on the concept (this taskforce felt that there was moderate or high certainty that ovarian screening has no net benefit or that the harms outweigh the benefits).[7]

Historical perspectives

The four international trials on ovarian cancer screening share certain major characteristics as outlined in Table 1.

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Table 1. Characteristics of the four international trials on ovarian cancer screening.[9]

Trial	Kentucky trial[4]	PLCO trial (USA)[2]	UKCTOCS trial (UK)[3]	SCSOCS trial (Japan)[5]
Design	Population control	Randomized control	Randomized control	Randomized control
Status	Ongoing	Closed	Closed	Closed
Accrual	Ongoing	November 1993–July 2001	April 2001–October 2005	September 1985–1999
Follow-up	Ongoing	Up to 13 years from enrollment	Up to 13.7 years from enrollment	Up to 17.3 years from enrollment
Duration of accrual	14 December 1987–present (28 + years)	1993–2001 (7.5 years)	2001–2005 (4.6 years)	1985–1999 (14.3 years)
Duration of screening	14 December 1987–31 January 2016 (28.1 years)	November 1993–July 2001 (7.7 years)	April 2001–October 2011 (10.7 years)	September 1985–December 1999 (14.2 years)
Follow-up	Up to 28.1 years	Up to 13 years	Up to 13.8 years	Up to 17 years
Eligibility	⩾50 years or ⩾25 with family history	55–74 years	50–74 years and postmenopausal status	Asymptomatic postmenopausal women
Group screened, n	44,930 USS	34,253[a] 34,304 control	50,084 MMS 50,060 USS 100,149 control	41,688 USS & Ca125 40,799 control
Total screens	276,282 USS	150,598	345,570 MMS 327,775 USS	156,747
Shift to early stages detected	Yes	No	Yes	Yes
Follow-up of EOC TP	Mean = 9.0 years, median = 8.3 years (0.7–25.4)	Not reported	Median = 11.1 years (0–12)	Mean = 9.2 years (3–14)
Survival benefit	Yes	No	Yes	Analysis pending
Control group	Yes	Yes	Yes	Yes

UKCTOCS: UK Collaborative Trial of Ovarian Cancer Screening; USS: ultrasound; MSS: multimodal strategy; EOC TP: Epithelial ovarian cancer true positive.
[a]USS alone followed by Ca125 alone.

Over 100,000 screens were administered in each trial and more than 30,000 women participated in each with the greatest enrollments and screens administered in the UKCTOCS and Kentucky trials. Ongoing accrual created differences in follow-up durations in these four trials with the result that the follow-up of individual participants was different not only between trials but also within each trial. Central measures description of the follow-up for ovarian malignancies detected by screening was reported in three of the four trials (Kentucky, UKCTOCS, SCSOCS (Shizouka Cohort Study of Ovarian Cancer Screening)) and leads to the expectation that more than half of the participating women were followed for 5 years, a surveillance interval that should be adequate for detecting a survival advantage associated with screening. Transvaginal ultrasound (USS) and Ca125 were utilized as screening tools in all four of the trials, but were applied differently. USS was the prime screening modality in the Kentucky and one arm of the UKCTOCS trials. A second arm of the UKCTOCS trial utilized a rising Ca125 algorithm that when abnormal was accompanied by a final confirmatory USS. The SCSOCS trial utilized simultaneous USS and Ca125 determinations at each screen. The PLCO trial utilized USS alone for the first several years and then completed the last 4 years of screening with Ca125 alone. Importantly, the screening tools applied in the Kentucky, UKCTOCS, and SCSOCS trials successfully identified early-stage malignancy, while the approach undertaken in the PLCO did not. Simultaneously enrolled participants who were not assigned to the screening group composed the control group in the PLCO, UKCTOCS, and SCSOCS trials, while the Kentucky trial compared survival data to unscreened Kentucky women presenting with ovarian cancers during the period that Kentucky screening was performed. Three of the trials are closed to accrual, while the Kentucky trial continues to accrue. In-depth reviews of all four trials have been published.[8,9]

The UKCTOCS trial reported in the *Lancet* paper[1] was a large, multi-institutional RCT conducted long enough for sufficient accrual and follow-up. The investigational team had experience with the screening tools dating back to 1988.[10] The trial employed a multimodal strategy (MMS) using the biomarker Ca125 combined with USS as a secondary test that was compared with USS alone. Ca125 assessments in the MMS arm were applied using significant increases above baseline over time and interpreted though a proprietary risk of ovarian cancer calculation (ROCA).[11] A priori estimation of 90% power for the 200,000 participants was sufficient at a two-sided 5% significance comparing no screening with both screening

arms. Annual screening was used with short-term re-examinations of abnormal results by MMS or USS and evaluation by a clinician. Participants were eligible for 7–11 screens depending on the time of entry. The major end-point was the duration of disease-specific survival from ovarian cancer after enrollment. Death records were obtained from national registries and also from direct communication with trial participants. Cases associated with the International Classification of Diseases (10th ed.; ICD-10) codes for ovarian malignancies were subjected to re-review by an expert panel to insure that they were appropriate for inclusion. Death due to ovarian cancer was based on site or size evidence of progression by imaging, clinical worsening, or rising biomarkers and included malignant neoplasms of the ovary designated by ICD-10 C56, including borderline epithelial ovarian cancers and fallopian tube malignancies, but not primary peritoneal cancers. Prevalent ovarian cancers were defined as demonstrating a change point in Ca125 levels prior to randomization and could be separately considered in the MMS group, presuming that an ovarian malignancy existed before screening was initiated.

The rigor of the analyses provided in the *Lancet* paper[1] is extremely high, paying strong attention to performing the same analyses used by the PLCO report[2] so that any differences in findings would not be related to the analytic approach. Importantly, the investigators in the *Lancet* paper performed analyses for different contingent assumptions and possibilities, complementing approaches using event censoring with treatments as competing risks.

Incident ovarian malignancies occurred at 0.6% over the course of the study and were equivalent in the MMS, USS, and the no-screening groups. These authors show a statistically significant reduction in *incident* cancer mortality in the MMS screening group relative to the unscreened group that increased with follow-up surveillance (8% reduction in years 0–7 vs 28% reduction in years 7–14). Kaplan–Meier analysis supported the observation of a screening survival benefit against a background of increasing mortality hazard in the no-screening arm throughout the study. Ancillary reports of high compliance (~80%), incidence in agreement with the general population, and low screening-related complications at surgery (~3%) indicate the soundness of the ovarian cancer screening approach as related in the *Lancet* report, which estimates that over time equivalent to the study's 13.6-year follow-up period, 641 screens would be needed to prevent one death from ovarian cancer.[1]

The investigational team responsible for the results presented in the *Lancet* paper should be congratulated on a thorough analysis demonstrating that screening for incident ovarian cancers reduces mortality due to this disease.

Commentaries on the *Lancet* paper in scholarly journals

Commentaries on the *Lancet* paper presented reservations about the UKCTOCS results or doubted the promise of this work,[12–16] while finding the secondary analyses on incident cancers and delayed survival effect "intriguing."[14] The statistically significant improved survival in the incident cancer analyses ($p = 0.021$) as well as the high sensitivity (i.e. percent of ovarian cancers detected) of detection within a year screening (84% MMS vs 73% USS) seemed under-appreciated in various commentaries,[15] while extending follow-up in order to discriminate greater significance to the delayed survival effect was generally supported. There was criticism that an early survival advantage was absent[12] and of the 59% detection rate by the MMS approach.[13] One commentary used unproven preconceived notions about both the exclusion of primary peritoneal cancers and prevalent cancers, as well as simulation and modeling to dismiss the results reported from the UKCTOCS, while challenging whether any positive effect was due to delaying ovarian cancer death rather than preventing it.[16]

Interpretations by the popular media in the first days after publication included quotes that were both highly positive and tempered and dismissive.[17–19] Reporting by the BBC called the work "encouraging" and "a potential landmark moment,"[20] but added, "The results are promising, but perhaps not all that promising,"[20] which can be interpreted to mean that the findings were "very encouraging" but there was "still more work to do."[20] It has been pointed out that "it is unlikely that a comparably sized study will ever be performed again owing to the expense and limited import of the findings."[14] Consequently, it is extremely important that the follow-up of the UKCTOCS be extended in order to determine if the delayed survival effect can be better established statistically.

There are several reasonable questions raised by the work reported in the *Lancet* paper:

1. *How similar is the performance of the two screening modalities: MMS versus USS?* The *Lancet* paper[1] reported 338 ovarian cancers detected by MMS with 190 alive and 148 having died, while 314 ovarian cancers were detected by USS with 160 alive and 154 having died. Chi-square testing of this overall result (MMS vs USS, variables: alive and died) does not show a significant difference between the two modalities ($p = 0.1786$). The end-point performance of either of the screening modalities was significantly different from the no-screening group (screening vs no screening: $p = .0017$ or individually (MMS, USS, no screening: $p = .00297$)). As stated in the *Lancet* paper,[1] results from analysis using the Cox proportional hazards model and the Royston–Parmar flexible parametric model gave small differences between MMS and USS modalities that were not statistically significant (estimated mortality reduction years 7–14: 23% MMS vs 21% USS). Differences between MMS and USS were not apparent using

the Weighted Log Rank (WLR) analysis. It is reasonable to conclude that the screening modalities MMS and USS performed similarly in the reported study (i.e. were not significantly different) and each yielded survival results significantly different from the no-screening group.

2. *What is the expected false negative rate associated with the MMS screening modality and in its application as a prevalence determination?* Slightly over 20% of ovarian cancers have been reported to lack Ca125 expression.[21,22] Lack of Ca125 expression has consequences because Ca125-negative ovarian malignancies cannot be expected to be detectable in the MMS group. An estimated correction for the 20% expected lack of Ca125 expression in the MMS group (n=237) that would appear falsely negative would predict 296 ovarian cancers and FNs=97 (false negative=FN) with a resultant sensitivity estimated at 67% for the MMS modality that is lower than the 73% sensitivity reported in the *Lancet* paper for USS.[1] In addition, Ca125-negative ovarian malignancies would also evade the test for prevalent ovarian cancers and are likely to result in the increased detection of late-stage ovarian cancers.

A special situation occurs when abdominal symptoms are present. Guidelines exist for the American generalist for collecting and evaluating information on symptoms related to ovarian cancer[23] as well as for British general practitioners.[24] These symptoms are quite general, and it is thought that virtually every woman will experience at least one of these symptoms at some time. Estimates in the Kentucky Ovarian Cancer Screening trial indicate that ~60% of women who do not have ovarian cancer will report one of these symptoms in agreement with observations involving British women.[25] This frequency is high enough to consider that it virtually expands surveillance for ovarian cancer to more than half of all women even though the actual incidence of ovarian cancer is quite low,[26] an expansion that is supported by advocacy to screen all women for BRCA1 and BRCA2 mutations[27,28] and by identification of an increased number of genes with germ line mutations associated with ovarian cancer risk.[29] The consequence of ignoring symptoms is likely to result in women symptomatic for ovarian cancer being diagnosed later with advanced disease.[30] Symptoms frequency and expansion of gene screening give a new face to ovarian cancer which is generally regarded to have a low incidence and lends considerable justification to the application of surveillance screening approaches knowing that survival benefits are certainly possible as reported in the *Lancet* paper.[1]

An expanding literature implicates the fimbriated end of the fallopian tube as the point of origin of ovarian cancer.[31–40] The developing hypothesis is that invasive or serous tubal intraepithelial carcinoma (STIC[31]) originating in the fimbriated ends of the fallopian tubes is responsible for seeding the ovaries and peritoneal cavity with malignant cells.[41] A challenge presented by this model is that it is founded on microscopic disease that is below the resolution of biomarkers and ultrasonography and consequently implies that these screening tools cannot be effective. However, the position indicated by other screening studies,[3–5] and the *Lancet* paper[1] is that these biomarker and ultrasonography screening modalities are sufficiently effective in detecting ovarian cancer early enough to decrease mortality and increase survival.[9] Thus, cases that have progressed beyond STIC in the distal fallopian tube can be detected by biomarker and ultrasonography screening often enough to achieve a favorable prognosis for extending survival.

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