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Original Research

Outcomes from ovarian cancer screening in the PLCO trial: Histologic heterogeneity impacts detection, overdiagnosis and survival

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Abstract ***Aim:*** A mortality benefit from screening for ovarian cancer has never been demonstrated. The aim of this study was to evaluate the screening outcomes for different histologic subtypes of ovarian cancers.
Methods: Women in the screening arm of the Prostate, Lung, Colorectal and Ovarian Screening Trial underwent CA-125 and transvaginal ultrasound annually for 3–5 years. We compared screening test characteristics (including overdiagnosis) and outcomes by tumour type (type II versus other) and study arm (screening versus usual care).
Results: Of 78,215 women randomised, 496 women were diagnosed with ovarian cancer. Of the tumours that were characterised (n = 413; 83%), 74% (n = 305) were type II versus 26% other (n = 108). Among screened patients, 70% of tumours were type II compared to 78% in usual care (p = 0.09). Within the screening arm, 29% of type II tumours were screen detected compared to 54% of the others (p < 0.01). The sensitivity of screening was 65% for type II tumours versus 86% for other types (p = 0.02). 15% of type II screen-detected tumours were stage I/II, compared to 81% of other tumours (p < 0.01). The overdiagnosis rate was lower for type II compared to other tumours (28.2% versus 72.2%; p < 0.01). Ovarian cancer–specific survival was worse for type II tumours compared to others (p < 0.01). Survival was similar for type II (p = 0.74) or other types (p = 0.32) regardless of study arm.

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Conclusions: Test characteristics of screening for ovarian cancer differed for type II tumours compared to other ovarian tumours. Type II tumours were less likely to be screen diagnosed, early stage at diagnosis or overdiagnosed.

1. Introduction

The majority of women with ovarian cancer present with advanced stage disease where long-term survival is rare [1]. Because early-stage ovarian cancer has significantly higher survival rates, early detection through screening to reduce mortality has been investigated for the last several decades. Screening for epithelial ovarian, fallopian tube and primary peritoneal cancers poses several challenges including the lack of a test with adequate specificity and the morbidity associated with false-positive tests. Despite several large prospective trials, a mortality benefit for screening women at average risk has not been demonstrated [2–5].

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was the largest prospective trial of ovarian cancer screening in the United States with over 78,000 female participants. Screening was performed using the biomarker CA-125 combined with transvaginal ultrasound (TVU). A mortality benefit of screening was not identified. Significant harms from ovarian cancer screening included the high rate of false-positive screens, 9.6%, of which 33% were followed by surgery [3]. The results of the larger UK Collaborative Trial of Ovarian Cancer Screening, which randomised 202,638 average risk women to no screening, annual TVU, or multimodal screening with serum CA125 interpreted with the risk of ovarian cancer algorithm followed by TVU when needed, demonstrated fewer complications but was likewise unable to demonstrate a reduction in mortality from screening for ovarian cancer. A possible delayed impact of screening will need to be confirmed with longer term follow-up [2].

Over the last decade, the emergence of robust clinicopathologic, molecular, and genetic data have enabled a more accurate, modern characterisation of ovarian cancer subtypes. The vast majority of ovarian cancers are epithelial ovarian cancers, which can be further subdivided into two main histological categories: Type I and type II tumours. Type II ovarian cancers are defined by *TP53* mutations and are the most common and most aggressive of the ovarian cancers. The corresponding histologies include high-grade serous (70%), high-grade endometrioid, carcinosarcoma, and undifferentiated carcinomas. Type I tumours are less aggressive than Type II and include low-grade serous, low-grade endometrioid, clear cell carcinomas, and mucinous carcinomas and are characterised by mutations in *KRAS*, *BRAF*, *PTEN*, *PIK3CA*, *CTNNB1*, *ARID1A*, *PPP2R1A* [6–10]. Each of these types has distinct risk factors and potential precursor lesions [9–11]. The even less aggressive ovarian low malignant potential tumours (LMP) tend to remain in the ovary and are rarely metastatic. Non-epithelial ovarian cancers are rare—the most common among adults are stromal cell tumours (e.g. granulosa cell tumours), which, like type I epithelial tumours tend to be slow growing.

These classifications of epithelial ovarian cancers into distinct phenotypes have the potential to influence the success of early detection and screening programs [12]. The impact of different rates of innate tumour growth can impact the efficacy and the harms of screening programs [13]. Presumably, the slow growing type I, LMP, and stromal cell tumours are more likely to be detected by screening, whereas a shorter window between early stage and metastatic disease is assumed for more aggressive type II cancers with higher stage at detection [13]. Early identification of type II tumours could potentially influence survival, whereas, identification of type I and non-epithelial ovarian cancers before the onset of symptoms is less likely to affect disease-specific mortality.

Previous analyses of ovarian cancer screening trials have not assessed outcomes accounting for the heterogeneity of behaviours of epithelial ovarian cancers. We used data from the PLCO trial to examine screening outcomes by tumour type. We undertook this study to determine how screening impacts the detection and overdiagnosis of type II ovarian tumours differentially from other types of ovarian cancers. In addition, we were interested in whether screening influences outcomes, including mortality, specifically for the more aggressive and lethal type II ovarian cancers.

2. Methods

The PLCO trial has been described in-depth previously [14]. Briefly, enrolment occurred between November 1993 and July 2001. Participants were eligible if they were aged between 55 and 74 years and had not been previously diagnosed with prostate, lung, colorectal or ovarian cancer. The trial recruited participants from 10 screening centres in the United States and targeted the general population living in the catchment areas. Institutional Review Boards approved the trial at each centre. Participants were randomised into the screening

or usual care arm and completed a self-administered survey at baseline, which included demographic information, medical history, basic risk factors and screening history.

Women randomised to the screening arm of the trial were offered annual ovarian cancer screening with TVU and a CA-125 blood test. Screening occurred at baseline and included an annual TVU for the following 3 years and CA-125 for the following 3–5 years depending on randomisation year (due to a change in protocol). Women randomised to the usual care arm were not offered any screening.

A CA-125 level $\geq$35 U/mL was considered a positive test. Abnormal TVU results were based on ovarian volumes >10 cm^3; cyst volume >10 cm^3; any solid area or papillary projection extending into the cavity of a cystic ovarian tumour of any size; or any mixed (solid and cystic) component within a cystic ovarian tumour. A letter was sent to women and their physicians with screening results specifically highlighting abnormal test results. Medical care conducted as a result of abnormal screens was managed by participants' physicians and was not under the trial's control.

All incident cancers and deaths were ascertained, primarily by means of a mailed Annual Study Update questionnaire. Follow-up for cancer incidence continued until February 28, 2010, or 13 years from randomisation, whichever came first. Medical records pertaining to diagnosed cancers were obtained by the screening centres and data on the stage, histology and grade of PLCO cancers were abstracted by certified tumour registrars. In addition, treatment information during the first year following diagnosis was abstracted. Deaths were identified through the Annual Study Update or linkage to the National Death Index and extended beyond the incidence data to December 31, 2012. With the extended mortality follow-up, women were followed for up to 13–19 years.

This analysis included all women diagnosed with ovarian, fallopian tube, or peritoneal cancer during the follow-up period for cancer incidence. Among women in the screening arm, cancers were considered screen detected if they were directly diagnosed as a result of a positive screening test. Interval cancers were those diagnosed within 12 months of a negative screening examination. Cancers diagnosed after the rounds of screening were considered post-screening.

2.1. Tumour subtypes

Tumour subtypes were classified based on histology and grade [6]. Tumours were defined as type II if they were moderately or poorly differentiated serous cystadenomas, cystadenocarcinomas, adenocarcinomas or carcinomas not otherwise specified; undifferentiated carcinomas; and carcinosarcomas. Type I tumours were defined as mucinous or clear cell cystadenocarcinomas and well-differentiated serous cystadenomas, serous

Table 1
Distribution of characteristics of women diagnosed with ovarian cancer in the Prostate, Lung, Colorectal, and Ovarian Screening Trial overall and by study arm (including LMP cases).

Patient characteristic	Total study population	Screening arm	Usual care arm	Chi-square p-value by arm
	N (%)	N (%)	N (%)	
Age at randomization				
55–59	125 (25.2)	69 (26.0)	56 (24.2)	0.45
60–64	152 (30.7)	73 (27.6)	79 (34.2)	
65–69	126 (25.4)	70 (26.4)	56 (24.2)	
70–74	40 (18.7)	53 (20.0)	40 (17.3)	
Race/ethnicity				
Non-Hispanic White	447 (92.5)	237 (91.5)	210 (93.7)	0.41
Other race/ethnicity	36 (7.5)	22 (8.5)	14 (6.3)	
Missing	13	6	7	
Education level				
<High school (HS) Graduate	33 (6.8)	17 (6.6)	16 (7.1)	0.77
HS Graduate/Post-HS Training	185 (38.3)	96 (37.1)	89 (39.7)	
Some college/college graduate/post-graduate	265 (54.9)	146 (56.4)	119 (53.1)	
Missing	13	6	7	
Family history of ovarian cancer	27 (5.6)	14 (5.4)	13 (5.9)	0.84
Screened for ovarian cancer in 3 years before trial	19 (3.9)	11 (4.2)	8 (3.6)	0.71
Total ovarian tumours detected	496 (100)	265 (53.4)	231 (46.6)	0.09
Type II tumour	305 (61.5)	159 (60.0)	146 (63.2)	
Other tumour types	108 (21.8)	67 (25.3)	41 (17.8)	
Unknown tumour type	83 (16.7)	39 (14.7)	44 (19.0)	
Ovarian-specific deaths	309 (100)	161 (60.7)	148 (64.1)	0.45
Type II tumour	214 (69.3)	114 (70.8)	100 (67.6)	
Other tumour types	31 (10.0)	18 (11.2)	13 (8.8)	
Unknown tumour type	64 (20.7)	29 (18.0)	35 (23.6)	

cystadenocarcinomas or adenocarcinomas. Tumours were considered "other" if they were described as LMP tumours, granulosa cell tumours or other stromal tumours. Confirmed ovarian cancers without sufficient evidence to categorise the tumour (e.g. "adenocarcinoma") were designated of unknown type and were not included in the main analysis.

2.2. Statistical analysis

We examined differences in the distribution of tumour type and stage by study arm (screening and usual care) and type of diagnosis (screen-detected, interval, post-screen, never screened, usual care arm). Because the objective of this analysis was to determine how screening influences outcomes and survival from type II malignancies differently from slower growing tumours, we combined "other" tumours with type I tumours.

We compared sensitivity and overdiagnosis by tumour type. Sensitivity was calculated as the number of screen-detected cases divided by the number of screen-detected plus interval cases. Overdiagnosis (cancers that never would have been detected without screening) rate was calculated for type II and other tumours by dividing the difference across trial arms in the number of tumours of that type detected during the total follow-up period by the number of screen-detected tumours of that type. We assessed differences in the distribution of tumour types, stage, sensitivity, and overdiagnosis rate using chi-square tests. We analysed potential differences in ovarian-specific cancer survival by tumour type and diagnosis type using Kaplan–Meier survival curves. All analyses were conducted using SAS 9.4.

3. Results

There were a total of 78,215 women randomised with 39,104 in the screening arm and 39,111 in the usual care arm. After excluding women with both ovaries removed by study baseline [n = 4852 (12.4%) screening arm; n = 4806 (12.3%) usual care arm], data were available for 34,252 women in the screening arm and 34,305 in the usual care arm. The rates of screening before the trial were low overall (3.9%) and did not significantly differ by arm. During the study period, 496 women (265 in screening arm and 231 in usual care arm) were diagnosed with ovarian cancer (Table 1). Age, race and ethnicity, education level and family history of ovarian cancer were similarly distributed between the arms among cases.

Approximately 61.5% of the tumours were type II, and 21.8% were classified as "other" tumour types (Table 1). There were 83 tumours overall (16.7%) that did not have sufficient information regarding histology or grade to be classified – 39 in the screening arm and 44 in the usual care arm (p = 0.20). Unknown tumours were excluded from subsequent analysis. The distribution of tumour types was not significantly different between study arms (p = 0.09). Overall, 70% of ovarian cancer-specific deaths were from type II tumours, whereas only 10% of deaths were from other tumour types; 20% of deaths were among women with unknown tumour types. The distribution of deaths did not differ by study arm (p = 0.45).

Among patients randomised to the screening arm, 28.9% of type II tumours were screen-detected compared to 53.7% of other tumours (Table 2). The remaining type II tumours were diagnosed post-screening (45.9%), as an interval diagnosis (15.7%), or among women never screened (9.4%). The distribution of detection categories for other tumours was significantly different from type II tumours (p < 0.01), with other tumours less likely to be diagnosed post-screening (25.4%) or as an interval diagnosis (9.0%). The estimated overdiagnosis rate was significantly higher for other types of tumours (72.2%) compared to type II (28.2%; p < 0.01). Results were similar after excluding LMP tumours. The sensitivity of screening was significantly lower for type II tumours (64.8%) than for other tumour types (85.7%; p = 0.02).

The majority of screen-detected type II tumours (84.8%) were diagnosed at advanced stages (III/IV), compared to only 20.0% of screen-detected other tumour types (p < 0.01). The distribution of stage did not differ by study arm for either type II or other tumour types (Table 3). Within both the screening and usual care arms, approximately 86% of type II tumours were diagnosed at stage III/IV (p = 0.96). Other tumours were much less likely to be advanced stage than type II tumours; 30.3% were stage III/IV in the screening arm and 39.5% in the usual care arm (p = 0.34).

Ovarian-specific survival was significantly worse for type II ovarian tumours compared to the other types of tumours diagnosed (p < 0.01) within the total study

Table 2
Characteristics of screening detection of ovarian cancers by tumour type within screening arm.

Detection type, n (%)	Type II tumours	All other tumours	p-value
Never screened	15 (9.4)	8 (11.9)	0.002
Screen-detected	46 (28.9)	36 (53.7)	
Interval	25 (15.7)	6 (9.0)	
Post-screening	73 (45.9)	17 (25.4)	
Sensitivity, (%)	64.8	85.7	0.02
Overdiagnosis, (%)	28.2%	72.2%	<0.001
Overdiagnosis, (%) (Excluding LMP tumours)	28.2%	80.9%	<0.001
Stage among screen detected, n (%)			
Stage I–II	7 (15.2)	28 (80.0)[a]	<0.001

Abbreviation: LMP, low malignancy potential.
[a] There was 1 other tumour type that did not have information on stage.

Table 3
Distribution of tumour types and tumour stage at diagnosis by screening arm in the PLCO.

Tumour type and stage	Screening arm	Usual care arm	p-value by study arm
	N (%)	N (%)	
Type II tumour			
Stage I–II	22 (14.2)	21 (14.4)	0.96
Stage III–IV	133 (85.8)	125 (85.6)	
Other tumour types			
Stage I–II	46 (69.7)	23 (60.5)	0.34
Stage III–IV	20 (30.3)	15 (39.5)	
p-value by tumour type	<0.001	<0.001	

population (Fig. 1). Between the two study arms, ovarian-specific survival did not significantly differ by arm for type II tumours ($p = 0.74$) or for the other tumours ($p = 0.32$), as shown in Fig. 2. Among patients with type II tumours in the screening arm, and there was no difference in survival if they were screen detected or not ($p = 0.91$).

4. Discussion

Screening for epithelial ovarian cancers in the general population has historically posed several seemingly insurmountable challenges: ovarian cancer is a rare disease in the general population with a lifetime risk of 1 in 70 women; a discernible premalignant lesion has been elusive; and the burden of a false-positive test includes stress to the patient and potential morbidity associated with oophorectomy [15]. A significant survival benefit to screening women at average risk has not been demonstrated despite large prospective randomised trials [2–5]. Because these screening trials predate a modern understanding of the nature of ovarian carcinogenesis, none of the trials defined type II ovarian cancer as the lesion of interest. Previous studies of screening in ovarian cancer have not examined detection by tumour subtype despite a wide range of biologic behaviours.

Type II ovarian cancers are the most biologically aggressive ovarian cancer tumour type with an overall poor survival [9,10]. The primary focus of this analysis was to determine whether screening for ovarian cancer alters the outcomes specifically for women with type II malignancies. The results of this study support the notion that non-type II ovarian cancers tend to remain in an early stage for some time, whereas type II cancers tend to spread rapidly and are more likely to be missed in the window of opportunity for early detection afforded by a screening test.

Our findings support differences in detection and outcomes by histologic subtype of ovarian cancer diagnosed, consistent with molecular evidence of heterogeneity of behaviour among ovarian cancer subtypes [10]. The test characteristics of CA-125 and ultrasound to detect ovarian cancer were markedly different for type II

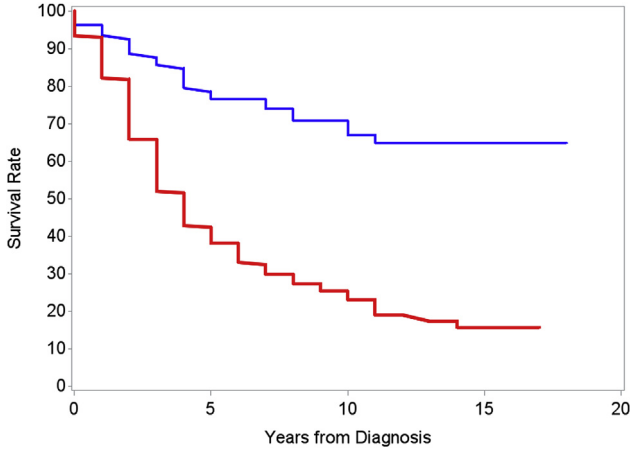

Fig. 1. Comparison of ovarian-specific survival between type II (red) and other tumour types (blue) in the Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

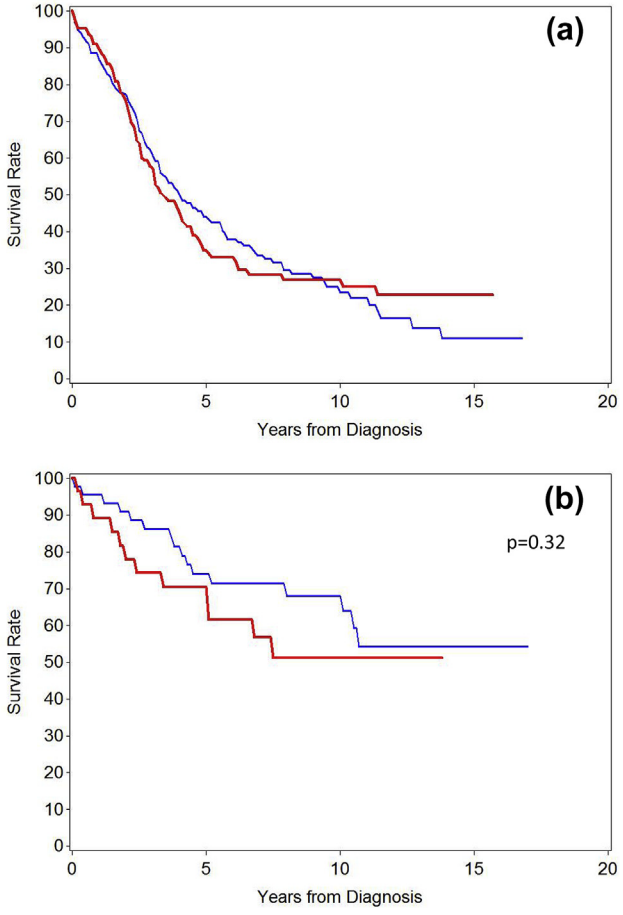

Fig. 2. Comparison of ovarian-specific survival by study arm for type II (a) and other types of ovarian tumours (b). Screening arm is blue and usual care arm is red (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

malignancies compared to other tumours. Type I and other malignancies had improved survival compared to type II tumours. Type II ovarian cancers were less likely to be detected through screening than other slower growing types of tumours, consistent with the known biologic behaviour of different ovarian cancers.

Although the UK Collaborative Trial of Ovarian Cancer Screening study did not reach statistical significance for its preplanned primary endpoint of mortality, a 15% reduction in ovarian cancer mortality was demonstrated in a secondary analysis suggesting a mortality benefit may emerge with longer follow-up [2]. This mortality benefit may be secondary to a stage shift and the next planned analysis of this trial will help to clarify whether this produced an improvement in outcomes. An examination of this trial by type of malignancy diagnosed will be crucial to a modern understanding of the role of screening in ovarian cancer.

Although most high-grade serous cancers are diagnosed at a late stage, those women with early-stage high-grade ovarian cancer have an overall good prognosis [16]. Early detection, through the identification of stage I disease could potentially improve outcomes for women with type II malignancies. Even without downstaging through ovarian cancer screening, early detection could potentially decrease the morbidity associated with primary debulking surgery and/or result in higher optimal cytoreduction rates or lower perioperative morbidity, which could also result in improved survival. The extent of disease present before surgery impacts the completeness of primary cytoreduction, which subsequently affects the survival for patients with advanced ovarian cancer [17]. Women with occult high-grade ovarian cancers detected incidentally have 5-year survival rates that are higher than those of women with clinically detected ovarian cancer [18].

Overdiagnosis is a potential harm of screening when disease is diagnosed that will never cause symptoms or death during a patient's lifetime [19]. As expected, we found substantially higher overdiagnosis of the slower growing tumours compared to type II. Updated, 15-year follow-up from the PLCO trial demonstrated no mortality difference between participants randomised to the screened arm compared to those in the usual care arm. However, within the screened arm, patients with a screen-detected cancer had higher survival rates than patients with otherwise detected ovarian cancer ($p = 0.04$, log-rank test). Survival at five years was 57.8% (screen-detected cases) versus 43.1% (non-screen-detected cases) [20]. We suspect that this survival difference is due to bias (e.g., overdiagnosis bias, lead-time bias, and length-biased sampling) for screen-detected cases. The preferential detection of biologically indolent cancers at an early stage without improved detection of biologically aggressive cancers at earlier stages will never provide the mortality benefit that is required for ovarian cancer screening to be effective.

Strengths of this study include the large size and prospective nature of the original cohort of this study. Robust long-term follow-up is available to evaluate long-term outcomes. Limitations however, must be acknowledged and include the time frame of the pathology reports. Because the cancers diagnosed during this study pre-date a contemporary understanding of the histopathologic differences between ovarian cancer types, close to 20% of tumours were unable to be characterised. Confirmatory pathologic review or molecular characterisation with immunohistochemistry was not performed for this analysis. In conclusion, tumour detection and tumour characteristics from screening were different for type II tumours compared to other ovarian tumours.

Even when accounting for ovarian cancer heterogeneity, a mortality benefit was not found within the PLCO for screening with CA-125 and TVU for the most aggressive and lethal type II ovarian cancers. Screening may have led to overdiagnosis of indolent ovarian tumours which may have been clinically detected or not detected at all with similar outcomes if not detected through screening. Screening modalities that reflect the biology of high-grade serous ovarian cancer as well better stratification by risk are urgently needed. Future studies of screening for ovarian cancer must incorporate a contemporary understanding of the natural history of ovarian cancer and account for the diverse biologic behaviour of the subtypes of this malignancy.

Conflict of interest statement

None declared.

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Author contributions

All authors contributed to study design, data interpretation and writing. Data analysis was primarily performed by EM and PP.

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