European Journal of Cancer 87 (2017) 182–188

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

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

Sarah M. Temkin [a,*], Eric A. Miller [b], Goli Samimi [b], Christine D. Berg [c], Paul Pinsky [b], Lori Minasian [b]

[a] *Division of Gynecologic Oncology, Virginia Commonwealth University, Richmond, VA, USA*
[b] *Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*
[c] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA*

Received 20 July 2017; received in revised form 30 September 2017; accepted 5 October 2017
Available online 21 November 2017

KEYWORDS
Ovarian cancer;
Cancer screening;
CA-125;
Overdiagnosis

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.

* *Corresponding author*: Virginia Commonwealth University, Department of Obstetrics and Gynecology, 1250 E Marshall Street Main Hospital, Rm 8-206, Richmond, VA 23298, USA. Fax: +1 804 828 3891.
E-mail address: sarah.temkin@vcuhealth.org (S.M. Temkin).

https://doi.org/10.1016/j.ejca.2017.10.015

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