Screening for ovarian cancer: is there still hope?

Stefanie Aust · Veronika Seebacher-Shariat

Received: 1 November 2019 / Accepted: 11 December 2019 / Published online: 27 January 2020
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Summary Mainly diagnosed at advanced stage, ovarian cancer still remains the most lethal gynecological malignancy. Regarding screening and early detection, ovarian cancer poses particular challenges. To date, no screening test has been proven capable of leading to a mortality benefit. In this short review, we summarize and discuss the underlying literature on screening for ovarian cancer, focusing on average-risk, asymptomatic women as well as women at high risk. We also discuss the continuous advances and limits in liquid biopsies for early detection and screening of ovarian cancer.

Keywords Fallopian tube cancer · BRCA · CA125 · Ultrasound · Liquid biopsies

Although ovarian cancer is rare with a lifetime risk of 1.3% and an incidence of 6.6 per 100,000 women per year, it is the 7th most common cancer and 6th most common cause of cancer death for women globally. In Europe, there were 67,771 new cases of ovarian cancer and 44,576 deaths in women in the year 2018. The majority of cases are diagnosed at an advanced stage, after the cancer has metastasized, leading to poor survival [1, 2]. The term ovarian cancer includes a heterogeneous group of malignant tumors arising from different precursor cells. The group of malignant nonepithelial ovarian tumors comprises germ cell tumors, sex cords stromal ovarian tumors, small cell car-

cinoma, malignant Brenner tumors, as well as ovarian carcinosarcoma. They are defined as “rare” and are diagnosed in <10% of all malignant ovarian tumors [3]. This review will primarily focus on screening for epithelial ovarian cancer, the most common type, further classified in high-grade serous (HGSOC), and the rare epithelial subtypes endometrioid, clear cell, mucinous, and low-grade serous carcinomas.

Screening and early detection

Two important components aiming at decreasing cancer mortality have to be distinguished: screening and early detection. Screening is applied in a healthy population to detect those individuals without symptoms, whereby particular criteria need to be considered such as tumor prevalence, positive and negative predictive value, safety of respective therapeutic consequences, and impact on morbidity and mortality. Early detection aims at reducing the rate of patients diagnosed in an advanced stage, focusing on detecting symptomatic patients as early as possible. As a heterogeneous disease with yet incomplete understanding of its pathogenesis, ovarian cancer poses particular challenges regarding the question of whether screening is possible or not. Different to other tumors, such as cervical cancer, ovarian cancers (especially HGSOC) seem to grow rapidly without the presence of yet detectable precursor lesions. Furthermore, following a positive screening test diagnosis of ovarian cancer requires surgical removal of the ovary, possibly leading to adverse events and side effects. Therefore, frequent and highly accurate tests are needed for effective screening strategies. Unfortunately, none of currently available tests fulfill these criteria. More importantly, to date no screening test for ovarian cancer has been proven capable of leading to a mortality benefit. Tests that have been evaluated for screen-

PD Dr. S. Aust, PhD ·
 Assoc. Prof. PD Dr. V. Seebacher-Shariat (✉)
 Department of Gynecology and Gynecologic Oncology,
 Medical University of Vienna, Waehringer Guertel
 18–20, 1090 Vienna, Austria
veronika.seebacher-shariat@meduniwien.ac.at

PD Dr. S. Aust, PhD
stefanie.aust@meduniwien.ac.at

ing are transvaginal ultrasound (TVU), measurement of serum CA-125, a tumor-associated antigen also known as MUC 16, and the combination of both. CA-125 is elevated in over 80% of women with advanced stage but in only up to 50% of women with early stage and its specificity is limited [4]. Elevated CA-125 serum levels are caused not only by ovarian cancer but by various other benign (endometriosis, inflammation) and malignant conditions and are dependent on other factors such as the menstrual cycle and smoking status. Furthermore, the ideal cut-off for further assessment is not completely clear. A case-control study revealed that half of the population developing ovarian cancer in the future had CA-125 levels greater than 30 IU/ml compared to only 7% of the control group [5]. This cut-off was further used in a screening protocol on 22,000 women leading to a specificity of 99.9%, a positive predictive value of 26.8%, and a sensitivity of 57.9% at two year follow-up [6]. The same study group consequently developed the risk of ovarian cancer algorithm (ROCA), a statistical model incorporating longitudinal changes in CA-125 over time in individual women [7]. Using samples of multiple cohort and randomized studies, a panel of other potential biomarkers, including CA-125, HE4, transthyretin, CA15.3 and CA72.4, was tested. However, the authors concluded that CA-125 remained the “single-best biomarker” for ovarian cancer [8].

Average-risk, asymptomatic women

To date results on morbidity, mortality and quality of life of four randomized controlled trials investigating screening versus no screening for ovarian cancer have been published [7, 9–12]. The two largest with results on overall survival are described here in more detail [7, 9]. The Prostate, Lung, Colorectal, and Ovarian (PLCO) trial evaluated the effect of screening on ovarian cancer mortality in 39,105 postmenopausal women using annual screens with serum CA-125 (threshold of 35 U/mL) and TVU compared to usual care ($n=39,111$) [9]. Neither stage distributions nor mortality of ovarian cancer differed between the groups. However, of the 1080 women who underwent surgical follow-up, 163 women experienced at least one serious complication (15%). The largest and most recent trial, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), enrolled 202,546 participants through 13 National Health Service Centers in England, Wales, and Northern Ireland. Included women were 50 to 74 years of age, postmenopausal and did not have increased risk of familial ovarian cancer [7]. Women were randomly assigned to 7 to 11 rounds of annual screening with transvaginal ultrasound alone, multimodal screening with CA-125 testing and TVU, or no screening at all. The ROCA was used for triaging women to further follow-up. Although a higher rate of low-volume disease (stage I, II and IIIA) was detected by multimodal screening

(119 [40%] of 299; $p<0.0001$) compared to no screening (149 [26%] of 574), mortality was nonsignificantly lower with TVU or multimodal screening (9% [–9 to 24], $p=0.31$ and 11% [8 to 26], $p=0.23$, respectively). In 44.2% of women without cancer screened in the multimodal group at least one test result was falsely positive. False-positive surgeries were done in 14 per 10,000 screens of multimodal and 50 per 10,000 screens of TVU screening. Complications occurred in 3.1 and 3.5% of women of the multimodal and TVU screening groups, respectively.

Women at high risk for ovarian cancer

Data on women with familial ovarian cancer syndrome are limited as randomized trials are ethically not acceptable. In the largest cohort study, the United Kingdom Familial Ovarian Cancer Screen Study (UK FOCCS), women with familial ovarian cancer syndrome who declined risk-reducing salpingo-oophorectomy (RRSO) were monitored annually with TVU and 4-monthly with CA-125 using the ROCA score [13]. Positive predictive value of incident screen was 25.5%, translating to four women needing surgery for each case of detected cancer. Among incident screen detected cancers, 30.8% were stage I or II. Nevertheless, screening cannot replace RRSO in women with genetic mutation leading to increased risk for ovarian cancer. A recent prospective study followed 1964 women carrying a BRCA 1 mutation [14]. There were 1814 women who had at least one screening ultrasound; 659 women had RRSO. The 10-year cumulative risk of death was 2.0% for women of the screening group compared to 0.5% for women who had RRSO (HR 0.23; 95% CI: 0.05–0.97; $p=0.05$). Most guidelines therefore do not recommend general screening in women with familial high risk for ovarian cancer. However, TVU and CA-125 measurement are considered reasonable for short-term surveillance starting at age 30–35 years until women chose to undergo RRSO [15].

Recent trends and prospects

Currently, “liquid biopsies” are a hot topic in cancer research. Circulating tumor cells, cell-free (cf) deoxyribonucleic acid (DNA), cf micro ribonucleic acid (microRNAs), or exosomes shed into the blood stream can be seen as surrogate for the tumor itself and are thus referred to as liquid biopsies. Liquid biopsies are derived from serum, plasma, or other body fluids and may provide noninvasive biomarkers. Their potential to improve early diagnosis is theoretically present but transition to clinic still far [16–18].

Several underlying biomarkers have been described for liquid biopsies in ovarian cancer [19–21] and might be interesting for a variety of clinical settings such as response evaluation and treatment selection. Nevertheless, sensitivity remains poor for screening and

early detection as the amount of circulating tumor genetic material is limited in early stage disease, and noncancer-derived mutations can cause false-positive results [22]. Another attempt is the measurement of methylations (epigenetic biomarker) in cfDNA as methylation occurs very early in malignant transformation. Methylation of RAS association domain-containing protein family 1 isoform A (RASSF1A) and proximal promoter of progesterone receptor (PGR-PROX) has been described to differentiate between benign and malignant ovarian tumors with a sensitivity of 80% and a specificity of 73% [23]. Hypermethylation of specific gene promoters has been measured in patients with early stage tumors with a sensitivity of 82% and a specificity of 100% (none in healthy controls) [24]. However, further validation and prospective trials are needed.

Another interesting concept aims at screening for exfoliated cancer cells or its putative precursor lesions, serous tubal intraepithelial carcinoma (STICs), not in the blood but in the uterine cavity by performing uterine lavage [25].

Taken together, there are several limitations that need to be overcome before implementing liquid biopsies into clinical decision making. Primarily, technical limitations such as standardization of isolation and quantification processes (e.g., cell-free DNA is higher in serum than in plasma), pre- and postanalytic quality control, and validation of the underlying assays. Second, after definition of biomarkers and underlying quality standards, clinical implication (impact on early detection and subsequently outcome and survival) has to be validated in large patient cohorts.

Conclusion

To date, missing evidence of mortality reduction and potential harm caused by screening are reasons to strongly advise against screening for ovarian cancer in the general population.

Take-home messages

- Currently, no evidence supports benefits of screening for ovarian cancer in the general population.
- Multimodal methods with serial measurements of CA-125 seem to outperform single threshold measurements of CA-125 or transvaginal ultrasound alone.
- There are several limitations that still need to be overcome before implementing liquid biopsies into clinical decision making.

Funding Open access funding provided by Medical University of Vienna.

Conflict of interest S. Aust and V. Seebacher-Shariat declare that they have no competing interests.

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