Editorial Commentary

Before it catches the eye…

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Epithelial ovarian cancer (EOC) is a relatively rare but lethal disease. While the lifetime risk in the general population is 1.3% with a median age of 65 years, women with a *BRCA1* and *BRCA2* mutation have a lifetime risk up to 40% and 18% respectively and develop EOC at a younger age (1,2). The most important reason for the high mortality in EOC is the fact that 80% of the patients are diagnosed at an advanced stage, when the cancer has spread throughout the abdominal cavity or beyond (FIGO stage III or IV) (1). The most common histotype is high-grade serous (63.4%) and patients with advanced stage disease have a 5-year survival rate of <30% (1,3). Despite lengthy and extensive efforts, researchers and clinicians have not succeeded in solving the problem of late detection of ovarian cancer by means of screening in population or high-risk groups (4-6). Women with a hereditary increased risk of ovarian cancer are therefore advised to have risk-reducing salpingo-oophorectomy (RRSO) performed in time, before the incidence rises (7,8). For patients who have not (yet) chosen for RRSO, the NCCN guideline states that '*ovarian cancer screening with transvaginal ultrasound combined with serum CA125 may be considered starting at age 30-35 years*' (7). The Dutch guideline does not recommend screening anymore (8). No preventive measures are advised for women without an increased risk.

Nebgen *et al.* have carried out a narrative review about ovarian cancer screening among postmenopausal women, 'by conventional and novel approaches' (9). They reviewed a (not specified) selection of studies on this topic, as they state '*in the context of new developments in the understanding of ovarian cancer biology*'. A total of five large studies were included that were published between 2008 and 2016. All studies included postmenopausal women without an increased risk for EOC, except for the Kentucky trial, which also included women from age 25 with a family history (10). Location of the studies was USA [3], UK [1] and Japan [1]. Three studies were RCTs, two were cohort studies and all five studies were large, including ten thousands of women. The screening method used was either annual transvaginal ultrasonography (TVU), with or without serum CA125 measurement, while two studies used multimodality screening by risk of ovarian cancer algorithm (ROCA) (4,11). They summarize: '*enhancing the sensitivity of two-stage strategies for early detection could reduce mortality from ovarian cancer*'.

Ovarian cancer-screening studies aim to find ways to detect asymptomatic EOC at an early, curable stage, to improve survival. However, up till now none of the studies showed a significantly reduced EOC mortality in the screened population. Some studies showed a (not significant) stage-shift to earlier stage disease, but not a survival benefit (9). Nevertheless, the authors of this review conclude that patients and clinicians remain interested in an effective screening tool for EOC and state that a two-stage multimodal-screening algorithm might show a long-term effect on mortality, although 'greater sensitivity is needed'.

Since 2001 the ovarian cancer paradigm has shifted to the fallopian tube as the origin of high-grade serous cancer (12). Mounting evidence showed that high-grade serous intra-epithelial tubal carcinoma (STIC) is the start of most (if not all) high-grade serous pelvic cancers (13).

This finding taught us clinicians to change our screening strategy accordingly. A STIC is too small to be visible at imaging, too small to produce substantial CA125 to increase the serum level, but not too small to disseminate and spread to the abdominal cavity. Prevalent EOC develops to metastatic disease, before it catches the eye. This is the new reality and the context in which ovarian cancer biology, symptomatology and screening should be interpreted. The authors do not seem to incorporate this paradigm shift in their review and recommendation. They wrote "*Epithelial ovarian cancers arise from simple flattened surface epithelial cells that cover the ovary, subserosal inclusion cysts, and/or the fimbriated end of the fallopian tube*". To the best of our knowledge, a precursor lesion of high-grade serous ovarian cancer has never been found in the ovarian surface epithelium itself, making it very unlikely that the ovarian surface epithelium is the start of the carcinogenesis (14). Even after almost two decades of prophylactic salpingo-oophorectomy and histo pathologic examinations according to the vigorous SEE-FIM protocol, the only precursor lesions of high-grade serous cancer (STICs) were detected in the distal end of the fallopian tube (15). Focusing on the ovary during the two-step screening by TVU will not help to detect EOC at an early stage, as early detection of EOC means the detection of a STIC. All further stages detected by TVU will not substantially change ovarian cancer mortality.

We agree with the reviewers that studies should focus on novel approaches to early detection. However, no significant benefit has been shown in prospective trials of protein markers, TP53 autoantibodies, microRNA panels, DNA promoter hyper methylation markers or ctDNA so far. It is questionable if STIC will ever produce detectable markers for early detection, as a STIC is a disseminating feature from the start. We therefore should stop focusing on two-step screening as TVU is more a diagnostic tool than a screening tool. Once the ovarian tumor is visible, the disease is mostly disseminated and survival rates are disappointingly low. Instead we should offer effective alternatives to prevent EOC mortality. For women with an increased risk, this means timely RRSO, before the incidence rises. Guidelines recommend risk-reducing surgery upon completion of childbearing to all women at a hereditary increased risk (7,8). Women with a *BRCA1* or *BRCA2* mutation are advised prophylactic salpingo-oophorectomy at the age of 35–40 and 40–45 years respectively (7,8). Nebgen *et al.* report that notwithstanding this guideline, uptake of RRSO is variable and despite lack of evidence for a survival benefit, the NCCN guideline allows for screening (9). However, it is questionable if '*does it not benefit it, then does it not harm*' is applicable for ovarian cancer screening. Although RRSO is recommended in high-risk women, the uptake is estimated to be no more than 60–70% (16). In the Netherlands, the uptake of RRSO before and after stopping ovarian cancer screening was studied by van Driel *et al.* (17). It turned out that as a result of counseling based on the guideline, the uptake of RRSO was high (81%), and it even increased further to 95% when screening wasn't offered anymore. It was concluded that screening high-risk women provides unjustified reassurance and deferral from timely RRSO. The increased patient awareness of the ineffectiveness of ovarian cancer screening led to a higher percentage of women undergoing RRSO within the recommended age range (17). For women at average risk, the effectiveness of screening is even lower than in a high-risk population. The large and well-designed UKCTOCS study did not show a survival benefit after 14 years (4). This led to the conclusion by the US preventative services task force (USPSTF) that screening for ovarian cancer in normal-risk women does not reduce mortality and is not recommended (18).

In conclusion, as mortality from EOC is the issue and not cancer detection, it is recommended to stop offering ovarian cancer screening with the two-step approach. A two-step screening (imaging after marker detection) is not the way to go, as tubal cancer spreads before it meets the eye. Instead, there is a need for studies on molecular markers for identification of early (STIC) lesions (19). In the meantime, effort should be put in prospective studies in women without an increased risk, evaluating the effectiveness and safety of opportunistic salpingectomy during abdominal surgery, either open or laparoscopically (20). For women at high-risk of EOC, screening should be omitted and counseling should be focuses on timely preventive salpingo-oophorectomy as the only proven safe option (21,22). In the future it is hoped that early salpingectomy, after childbearing, and delayed oophorectomy will be proven safe, to overcome side effects of early surgical menopause (23).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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