Ultrasound Screening for Ovarian Cancer: Are We There Yet?

Sharon E. Robertson, MD, MPH; Jeffery F. Peipert, MD, PhD

Drs. Robertson and Peipert are from the Department of Obstetrics & Gynecology at the Indiana University School of Medicine, Indianapolis, IN

Approximately 14,000 women die from ovarian cancer each year.¹ Despite decades of research, the overall 5-year survival rate from this disease remains disappointingly low at less than 50%.² Women who are diagnosed with localized disease have a chance to be cured of disease, with 5-year survival rates exceeding 90%. Unfortunately, the majority of women present to care with advanced disease owing to the asymptomatic nature of early ovarian cancer. There is yet to be a widely implemented screening test for this lethal disease. Four prior clinical trials have reported outcomes of various screening algorithms for ovarian cancer.³⁻⁶ Three of these trials found a shift toward earlier stage at diagnosis in their respective screened populations.⁴⁻⁶ After excluding prevalent cases of ovarian cancer, analyses from the United Kingdom Collaborative Trial of Ovarian Cancer Screening showed a survival advantage in their multimodal screening group.⁴ However, no trial has definitively shown an improvement in survival because of routine screening in a population of asymptomatic, low-risk women. Without data supporting an improvement in overall survival for women with ovarian cancer, implementation of a screening protocol is ill advised. Indeed, this year the U.S. Preventive Services Task Force again issued a Grade D recommendation against routine screening for ovarian cancer.⁷

In this issue of Obstetrics & Gynecology, van Nagell et al (see page 1091) report the results of their impressive ovarian cancer screening trial conducted over a span of 30 years.⁸ More than 46,000 asymptomatic women were prospectively screened for ovarian malignancy with annual pelvic ultrasound examinations. Abnormal ultrasound findings were followed up with tumor morphology indexing, CA 125 testing, and surgery as indicated. Six hundred ninety-nine surgeries were performed to detect 109 malignancies, with an overall complication rate of 8.3% (only five patients experienced a grade 4 complication). The authors report favorable test statistics, notably a positive predictive value of 15.6%, which is well above the generally accepted 10% cutoff for an ovarian cancer screening test. However, this screened cohort had a surprisingly high incidence of ovarian cancer (271/100,000 women vs 11.4/100,000 in the general population²), which improves the positive predictive value. When the test sensitivity and specificity as reported in this trial are applied to the general population, the positive predictive value falls to an unacceptable 0.7%.

The authors next retrospectively compare the women with epithelial ovarian cancer identified by screening with a cohort of women diagnosed with an ovarian malignancy who were referred to the University of Kentucky between 1995 and 2017. They report an intriguing shift toward earlier stage at diagnosis in their screened cohort as compared with the nonscreened population. Sixty-three percent of women in the screened population were diagnosed with

This is the author's manuscript of the work published in final edited form as:

Robertson, S. E., & Peipert, J. F. (2018). Ultrasound Screening for Ovarian Cancer: Are We There Yet? *Obstetrics and Gynecology*, 132(5), 1089–1090. <https://doi.org/10.1097/AOG.0000000000002962>

localized or regional disease compared with 30% in the unscreened cohort. Similarly, Surveillance, Epidemiology, and End Results (SEER) Program data from 2008 to 2014 show that 35% of ovarian cancers were detected at a local or regional stage, suggesting that the comparison cohort in this study is comparable with the U.S. population of patients diagnosed with ovarian cancer.

However, are we comparing apples to apples? The gold standard of research design would be a randomized controlled trial (RCT), and even in an RCT the reader should look for a Table 1 comparing the two groups. It is important to point out that there are important key baseline differences in the screened cohort compared with the referred (comparison) group. Among the screened population, 23% of women reported a family history of ovarian cancer and 43% reported a family history of breast cancer. The authors acknowledge that routine testing for genetically linked ovarian cancers was not performed. Given the large percentage of patients who reported a family history of breast or ovarian cancer, it is plausible that the screened cohort contains an unbalanced proportion of genetically related ovarian cancers as compared with the unscreened population. The United Kingdom Familial Ovarian Cancer Screening Study recently reported a shift in stage at diagnosis of ovarian cancer among women at high risk who were screened with a CA 125 test and ultrasonography.⁹ Further, 27% of malignancies in the screened cohort were type I tumors (including low-grade and clear-cell histologies), which typically are diagnosed at a lower stage and would again influence the reported stage shift in the positive direction. Although the screened population in this report is likely not reflective of the general population, we agree with the authors' conclusion that ultrasound screening in women at high risk for ovarian cancer may lead to earlier detection of disease.

Finally, van Nagell et al report that, as compared with their comparison referral cohort, the screened population had significantly improved disease-specific survival (79+/-4% vs 45+/-2% 5-year disease-specific survival). This survival difference remained true for both the entire cohort as well as those with type I and II malignancies separately and was entirely accounted for by the shift toward earlier stage at diagnosis.

The reader should use caution in the interpretation of these results. In the current study, the screened population has a higher percentage of type I tumors (27%) as compared with nationally reported data (11% of nationally reported ovarian malignancies from 2011 to 2015 were type I tumors²), and the specific histology of type I tumors in the control referral cohort is not reported. Additionally, genetic analysis is not readily available, despite a high percentage of women with a significant family cancer history. Each of these factors could influence disease-specific survival rates. In the absence of an RCT study design, we are unable to determine whether the presence of these and other potentially undetected confounding variables account for the differences reported, or whether a true difference in disease-specific survival is present with routine screening. Finally, we must again highlight that the screened cohort appears to represent a population of women at high risk for ovarian cancer, whereas the control referral cohort's risk is unknown. For these reasons, we cannot confidently agree with the authors' conclusion that the ultrasound screening reduced ovarian cancer mortality.

In conclusion, we applaud the authors for the completion of a landmark study that is impressive in scope and longevity. As purported by the authors, we agree that an ovarian cancer screening algorithm for women at high risk of developing ovarian cancer may detect this devastating disease at an earlier, potentially more treatable stage. However, the evidence that screening for ovarian cancer improves survival remains elusive. More evidence is needed before we adopt a widespread screening program.

Financial Disclosure Dr. Peipert has served on Advisory Boards for CooperSurgical/Teva and has received research funding and support from Merck, Bayer, and CooperSurgical/Teva. The other author did not report any potential conflicts of interest.

References

1. National Cancer Institute. Cancer stat facts: ovarian cancer. Available at: <https://seer.cancer.gov/statfacts/html/ovary.html> Retrieved August 23, 2018.
2. National Cancer Institute. SEER cancer statistics review 1975-2015. Available at: https://seer.cancer.gov/csr/1975_2015/browse_csr.php?sectionSEL=21&pageSEL=sect_21_table_08 Retrieved August 23, 2018.
3. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. *JAMA* 2011;305:2295-303.
4. Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 2016;387:945-56.
5. Kobayashi H, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. *Int J Gynecol Cancer* 2008;18:414-20.
6. van Nagell JR Jr, Miller RW, DeSimone CP, Ueland FR, Podzielinski I, Goodrich ST, et al. Long-term survival of women with epithelial ovarian cancer detected by ultrasonographic screening. *Obstet Gynecol* 2011;118:1212-21.
7. Henderson JT, Webber EM, Sawaya GF. Screening for ovarian cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2018;319:595-606.
8. van Nagell JR Jr, Burgess BT, Miller RW, Baldwin L, DeSimone CP, Ueland FR, et al. Survival of women with type I and II epithelial ovarian cancer detected by ultrasound screening. *Obstet Gynecol* 2018;132:1091-1100.
9. Rosenthal AN, Fraser LSM, Philpott S, Manchanda R, Burnell M, Badman P, et al. Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom familial ovarian cancer screening study. *J Clin Oncol* 2017;35:1411-20.