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Ovarian cancer think tank: An overview of the current status of ovarian cancer screening and recommendations for future directions

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ABSTRACT

Early diagnosis and screening of ovarian cancer remain significant challenges to improving patient outcomes. There is an urgent need to implement both established and modern strategies to address the "early detection" conundrum, especially as new research continues to uncover the complexities of the disease. The discussion provided is the result of a unique research conference focused on reviewing early detection modalities and providing insight into future approaches.

1. Introduction

In September 2023, the University of Colorado convened for the second Ovarian Cancer Innovations Group Think Tank, "Addressing the Impossible in Ovarian Cancer." To establish new directions of innovation in ovarian cancer research, experts reviewed the latest data on screening and early detection. The highlights of the meeting are reviewed in two categories – Screening and Early Detection. In general, screening refers to testing those without symptoms in an effort to prevent disease while early detection refers to testing in an effort to diagnose disease earlier and therefore improve outcomes. In the context of tubo-ovarian carcinoma, there is significant overlap in these categories as the outcome of the published research on screening is most often detection of disease and not its precursor.

2. Screening

The US Preventive Services Task Force does not currently recommend screening for ovarian cancer in asymptomatic women of average risk, citing its relative rarity (US Preventive Services Task Force, 2018). As low prevalence significantly decreases the positive predictive value of any diagnostic test, the risk of universal screening is false positive results, leading to distress and diagnostic surgery with potentially harmful complications. The UKCTOCS trial by Menon et al. is the largest randomized controlled trial on ovarian screening, including over 200,000 postmenopausal women. The investigators found that while annual multimodal screening (MMS) with a longitudinal serum CA-125 algorithm and/or transvaginal ultrasound (TVUS) resulted in a significant reduction in the diagnosis of advanced-stage ovarian cancer, there was no reduction in disease-specific mortality (Menon et al., 2021).

Dr. Usha Menon presented the results from an exploratory analysis of UKCTOCS patients with tubo-ovarian high-grade serous carcinoma (HGSC). Nine years after the screening period, MMS was associated with a 24.5 % decrease in the diagnosis of stage IV cancer, accompanied by a 47.0 % increase in the diagnosis of stage I disease. Among 259 participants in the MMS group and 520 participants in the no-screening group diagnosed with HGSC, fewer participants in the MMS group were diagnosed with advanced-stage disease than in the no-screening group (75 % vs 86 %, respectively; $P = .0003$). They found improvement in treatment-related outcomes among the patients screened with MMS: more had primary surgery (61 % vs 42 %, respectively; $P < .0001$), more had zero residual disease following debulking surgery (46 % vs 30 %,

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respectively; P <.0001), and more received the standard treatment, including both surgery and chemotherapy, rather than supportive care (74 % vs 64 %, respectively; P =.0032). With a median follow-up of 9.51 years, MMS was associated with an absolute difference in survival of 6.9 % (P =.042) at 18 years, 21.0 % (95 % CI, 15.6 %–26.2 %) in the MMS group compared with 14.0 % (95 % CI, 10.5 %-17.4 %) in the no-screening group (Menon et al., 2023).

The UKCTOCS exploratory analysis is encouraging, suggesting that earlier detection *can* impact mortality. The authors acknowledge limitations to the analysis, namely that the women in the trial were treated in the period 2001 to 2011 which was prior to advances in targeted therapies that have improved outcomes. Additionally, they note that lead time bias cannot be fully excluded as well as the lack of more granular molecular and/or genetic data that could provide additional context to the outcome data. Researchers and clinicians may wish to consider the value of screening on clinical endpoints beyond downstaging. However, given current evidence, these endpoints cannot yet be used as surrogates for disease-specific mortality. The trial highlights the need for adaptive screening trials that efficiently evaluate multiple clinical outcomes beyond the traditional outcome of survival.

Dr. Ashley Greenwood discussed the findings of her recently published systematic review on early ovarian cancer detection (Greenwood et al., 2022). Greenwood et al reviewed 131 peer-reviewed primary research articles evaluating the performance of a number of novel biomarkers including proteins, epigenetic changes such as microRNAs, DNA mutational profiles, RNA, and metabolites. The authors note that many studies combining novel biomarkers with those in practice (CA-125 and HE4) indicate a trend toward benefit over single-marker testing demonstrated by an AUC over 0.9. However, data show most candidate biomarkers (e.g. CA-125, human epididymis protein 4 [HE4], mesothelin, B7-H4, decoy receptor 3 [DcR3], and spondin 2) are not sufficiently elevated early in disease progression to be useful in detecting early-stage cancer. As in the UKCTOCS trial, longitudinal biomarker algorithms, such as CA-125 profile over time, can improve the performance of screening biomarkers and should be explored where appropriate.

Dr. Kathleen Moore presented on “the next era of biomarker discovery aimed at disrupting the natural history of epithelial ovarian cancer.” She discussed the role of population-based genetic screening for pathogenic variants, emphasizing that using incident cases of ovarian cancer as the impetus for genetic testing will only capture 20–30 % of pathogenic variants. Dr. Christine Walsh presented a community-based outreach program aimed at increasing the uptake of genetic counseling and testing in the high-risk Ashkenazi Jewish population.

Despite the breadth of research presented, screening remains challenging due to two primary factors: inability to sample tissue without invasive surgery and the low incidence of disease. As previously mentioned, the USPSTF makes particular mention of the rarity of ovarian cancer impacting the recommendation against screening. Dr. Kian Behbakht distilled the extent to which incidence affects the performance of a screening test. He pointed out that with an incidence of 0.09 %, even a test with 90 % specificity and 90 % sensitivity will yield a positive predictive value of 1 %. In the context of tubo-ovarian carcinoma, this could potentially mean that 99 women will undergo diagnostic laparoscopy for a false positive test to diagnose one case of carcinoma. For context, the incidence of carcinoma was 0.0074 % in the UKCTOCs study.

Distillation: Ovarian cancer researchers continue to grapple with how to screen for a rare disease that overwhelmingly presents in late stages. The research presented emphasizes that screening is not a lost cause, given improvements in treatment outcomes and the trend in survival with downstaging. The consensus among participants is that there is not adequate evidence for screening, but that the evidence to date indicate a persistent need for screening trial design that evaluates dynamic clinical endpoints in a rapidly changing therapeutic enviroment. There is work to do in identifying biomarkers that will improve patient outcomes. Identifying additional pathogenic genetic variants is key to informing genetic screening and targeted prevention. Subsequently, the identification of individuals at increased genetic risk offers important opportunities to reduce incidence and mortality. Innovative strategies to improve adherence to genetic screening guidelines are urgently needed.

3. Early detection

Dr. Barbara Goff presented on symptom-based screening in ovarian cancer, having conducted a national survey of over 1700 women (70 % with stage III or IV disease). Results showed that 95 % of women experienced symptoms before diagnosis and that a staggering 89 % of women with stage I or II disease reported symptoms (Goff et al., 2007). A subsequent case-control study in women undergoing surgery for ovarian masses found that women with cancer were significantly more likely to have specific symptoms and these symptoms typically were of recent onset and occurred frequently (Goff et al.). Survey data revealed that symptoms associated with early-stage disease were present for less than one year in duration but occurred more than 12 days per month. These included pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating/feeling full. A symptom index was developed based on the results of this study; performance statistics for the index revealed a sensitivity of 56.7 % for early-stage disease and 79.5 % for advanced-stage disease and a specificity of 90.0 % for women more than 50 years and 86.7 % for women less than 50 years.

In addition to her landmark study, Dr. Goff reviewed evidence that symptom recognition by patients and practitioners has the potential to increase early diagnosis of ovarian cancer. A challenge lies in identifying tools to assist front-line healthcare providers in recognizing symptoms and identifying patients needing additional screening. Primary care in the United States faces severe and worsening provider shortages and the burden of health care maintenance and documentation (McMahon et al., 2021). Thus, it is not a simple ask of an overburdened primary care system to reliably register and evaluate the constellation of symptoms associated with a rare disease. However, technology can lessen the burden and enable reliable symptom recognition. Electronic health record (EHR) software and patient-reported symptom-tracking software are tools that may notify providers when concerning patterns of symptoms arise. Machine learning and artificial intelligence (AI) offer promise for harnessing readily available data. For example, a recent web-based survey on shopping patterns before an ovarian cancer diagnosis demonstrated how purchases for products linked to potential symptoms can be analyzed using machine learning and employed as a strategy to help diagnose ovarian cancer earlier (Dolan et al., 2023). Also, AI can collate data regarding symptoms, family history, medications, and risk factors, alerting PCPs to potential risk and suggesting evaluation with CA-125 and ultrasound.

Dr. Moore discussed circulating tumor DNA (ctDNA) and its potential diagnostic value for early-stage tubo-ovarian cancer. Similar to the challenges with biomarkers, data suggest that at early stages ctDNA may not be present at levels high enough for usefulness. Dr. Moore emphasized emerging studies suggesting that ctDNA may have greater utility in treatment monitoring. Lheureaux et al. published findings from a phase II randomized control trial showing that sequencing ctDNA throughout treatment in epithelial tubo-ovarian cancer can demonstrate genetic mutations with 74 % sensitivity when compared with tumor whole exome sequencing (WES). Also, ctDNA detected new mutations not identified on WES, potentially adding insight into mechanisms of emerging treatment resistance (Lheureux et al., 2023).

TVUS is considered a first-line imaging modality for the evaluation of ovarian masses, but TVUS alone lacks adequate sensitivity and specificity for the early detection of ovarian cancer. This contributes to the fact that HGSC originates in the fallopian tubes, the anatomical position of which makes visualization difficult via TVUS. Imaging techniques must have excellent sensitivity to be effective tools for early diagnosis.

Computed tomography (CT), positron emission tomography–computed tomography (PET-CT), and magnetic resonance imaging (MRI) are often used to diagnose ovarian masses and offer greater sensitivity than TVUS, but they lack the sensitivity to diagnose STIC lesions reliably and are labor-intensive and costly. Dr. Karthik Sundaram presented innovative approaches to improve TVUS as the first-line diagnostic modality in the early detection of tubo-ovarian malignancies, including radiomics and machine learning as well as functional and molecular imaging. Dr. Sundaram discussed his ongoing original research into photoacoustic imaging with exogenous agents. His research collaborations focus on the theranostic use of micelles in order to deliver small molecule near-infrared dyes for the purpose of photoacoustic imaging, in an effort to detect early tubo-ovarian malignant and pre-malignant lesions. These dyes also demonstrate photothermal therapeutic effects which may be useful for treatment applications in the context of metastatic disease (Tian et al., 2024). He additionally highlighted ongoing research to improve the sensitivity of CT, PET-CT, and MRI. Despite current drawbacks, these imaging techniques can be useful in early detection. The combined use of EHR and AI may also prove useful in identifying patients who may benefit from this type of screening. The use of these imaging techniques in routine clinical practice, however, is complicated by cost and access. High-cost imaging is inaccessible to many and has the potential to worsen cancer-related financial toxicity for patients experiencing baseline socioeconomic distress.

Distillation: Given the poor outcomes in late-stage tubo-ovarian cancer, there is an urgency to increase early detection and improve outcomes. Research demonstrates that patients experience symptoms even in early-stage disease; however, additional work is needed to harness present and future technologies to capture symptoms in early-stage patients effectively. Liquid biopsy through ctDNA may offer a more promising monitoring modality. Research in imaging for the early detection of tubo-ovarian cancer is ongoing and includes using nanoparticles and protein conjugates. However, imaging modalities are costly and have the potential to risk financial toxicity without proven benefits.

4. Conclusions

The research presented at the University of Colorado's Ovarian Cancer Innovations Group Think Tank meeting was focused on future opportunities for ovarian cancer screening and early detection. The discussed advancements in novel data analysis and emerging technologies represent promising paths forward. Gathering experts from diverse thought and training backgrounds to address and report on specific questions is a valuable strategy to accelerate innovation.

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Author contributions

Julia M. Dexter contributed original draft and review and editing. Lindsay W. Brubaker and Benjamin G. Bitler contributed investigation, visualization, review and editing, supervision, and project administration. The remaining authors Barbara A. Goff, Usha Menon, Katherine N. Moore, Karthik M. Sundaram, Christine S. Walsh all contributed investigation, visualization and review and editing. Saketh R. Guntupalli contributed funding acquisition. Kian Behbakht contributed investigation, visualization, writing (review and editing), supervision, project administration and funding acquisition.

CRediT authorship contribution statement

Julia M. Dexter: Writing – review & editing, Writing – original draft. **Lindsay W. Brubaker:** Writing – review & editing, Visualization, Supervision, Project administration, Investigation. **Benjamin G. Bitler:** Writing – review & editing, Visualization, Supervision, Project administration, Conceptualization. **Barbara A. Goff:** Writing – review & editing, Visualization, Investigation. **Usha Menon:** Writing – review & editing, Visualization, Investigation. **Katherine N. Moore:** Writing – review & editing, Visualization, Investigation. **Karthik M. Sundaram:** Writing – review & editing, Visualization, Investigation. **Christine S. Walsh:** Writing – review & editing, Supervision, Investigation. **Saketh R. Guntupalli:** Funding acquisition. **Kian Behbakht:** Writing – review & editing, Visualization, Supervision, Project administration, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Dolan, E.H., Goulding, J., Tata, L.J., Lang, A.R., 2023. Using shopping data to improve the diagnosis of Ovarian cancer: computational analysis of a web-based survey. JMIR Cancer. 31 (9), e37141.

Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of Symptoms of Ovarian Cancer in Women Presenting to Primary Care Clinics.

Goff, B.A., Mandel, L.S., Drescher, C.W., Urban, N., Gough, S., Schurman, K.M., et al., 2007. Development of an ovarian cancer symptom index. Cancer 109 (2), 221–227.

Greenwood, A., Woodruff, E.R., Nguyen, C., Piper, C., Clauset, A., Brubaker, L.W., et al., 2022. Early Ovarian cancer detection in the age of fallopian tube precursors: a systematic review. Obstet. Gynecol. https://doi.org/10.1097/AOG.0000000000005496.

Lheureux, S., Prokopec, S.D., Oldfield, L.E., Gonzalez-Ochoa, E., Bruce, J.P., Wong, D., et al., 2023. Identifying mechanisms of resistance by circulating tumor DNA in EVOLVE, a phase II trial of cediranib plus Olaparib for Ovarian cancer at time of PARP inhibitor progression. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 29 (18), 3706–3716.

McMahon, L.F., Rize, K., Irby-Johnson, N., Chopra, V., 2021. Designed to fail? the future of primary care. J. Gen. Intern. Med. 36 (2), 515–517.

Menon, U., Gentry-Maharaj, A., Burnell, M., Singh, N., Ryan, A., Karpinskyj, C., et al., 2021. Ovarian cancer population screening and mortality after long-term follow-up in the UK collaborative trial of Ovarian cancer screening (UKCTOCS): a randomised controlled trial. Lancet 397 (10290), 2182–2193.

Menon, U., Gentry-Maharaj, A., Burnell, M., Ryan, A., Singh, N., Manchanda, R., et al., 2023. Tumour stage, treatment, and survival of women with high-grade serous tubo-ovarian cancer in UKCTOCS: an exploratory analysis of a randomised controlled trial. Lancet Oncol. 24 (9), 1018–1028.

Tian, Y., Carrillo-Malani, N., Feng, K., Miller, J., Busch, T.M., Sundaram, K.M., et al., 2024. Theranostic phthalocyanine and naphthalocyanine Nanoparticles for photoacoustic imaging and photothermal therapy of tumors. Nanotheranostics 8 (1), 100–111.

US Preventive Services Task Force, Grossman DC, Curry SJ, Owens DK, Barry MJ, Davidson KW, et al. Screening for Ovarian Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2018 Feb 13;319(6):588.