EDITORIAL

New Insights in Endometriosis Subtypes and Ovarian Cancer Risk

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In 2024, an estimated 19 680 new ovarian cancers and 12 740 ovarian cancer–related deaths will occur in the US.[1] Early detection continues to be elusive and screening strategies inadequate, even in women at high risk. Women continue to be diagnosed with advanced-stage disease, which portends a poor prognosis[2,3] despite improved outcomes in women treated with a poly (adenosine diphosphate-ribose) polymerase inhibitor for maintenance therapy, particularly those with germline or somatic *BRCA1* or *BRCA2* sequence variations.

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Multiple risk factors have been associated with epithelial ovarian cancer, including age, early menarche or late menopause, nulliparity, family history of breast or ovarian cancer, and *BRCA1* and *BRCA2* sequence variations.[4-7] More recently, additional genetic variants in the homologous recombinant pathway, including *BRIP1*, *RAD51C*, and *RAD51D*, have been associated with an increased risk of ovarian cancer.[8]

In 1925, Sampson first reported an association between endometriosis and epithelial ovarian cancer.[9] Since this initial report, data have emerged demonstrating an increased risk of ovarian cancer in women with endometriosis.[10,11] A clear association with clear cell, endometrioid, and low-grade serous histologies have been shown in some studies, although the relationship to high-grade serous carcinoma has been variably reported. In 2021, a systematic review and meta-analysis (24 studies) reported a 2-fold increased risk for ovarian cancer in women with endometriosis compared with those without (summary relative risk, 1.93 [95% CI, 1.68-2.22]). The association varied based on histologic subtype, particularly clear cell (3.44 [95% CI, 2.82-4.20]) and endometrioid (2.33 [95% CI, 1.82-2.98]) carcinoma.[12] Additionally, a 2024 population-based study utilizing the US National Inpatient Sample explored the relationship between endometriosis and the risk for ovarian, endometrial, cervical, and breast cancers. Multivariate analysis demonstrated an increased risk for ovarian (adjusted odds ratio, 3.34 [95% CI, 2.97-3.75]) and endometrial cancer in women with endometriosis compared with those without.[13]

Although multiple studies have demonstrated an association between endometriosis and histologic subtypes of epithelial ovarian cancer, there has been a paucity of data exploring the relationship between type or phenotype of endometriosis and epithelial ovarian cancer.

In a population-based study of 50 000 Finnish women with surgically verified endometriosis, investigators reported an increased risk of ovarian cancer (1.76 [95% CI, 1.47-2.08]). Furthermore, the increased risk was more significantly associated with endometrioid and clear cell carcinoma, 3.12 and 5.17, respectively. The subtype of endometriosis (eg, ovarian, peritoneal, and deep infiltrating) associated with ovarian cancer risk was highest for ovarian endometriosis, particularly endometrioid (4.72 [95% CI, 2.75-7.56]) and clear cell (10.1 [95% CI, 5.50-16.9]) carcinoma. There was no statistically significant association with deep infiltrating endometriosis and ovarian cancer; however, there were only 3 patients with deep infiltrating endometriosis in the cohort.[14]

In this issue of *JAMA*, Barnard and colleagues[15] eloquently present a population-based study exploring the association of endometriosis and endometriosis subtypes with the incidence of ovarian cancer overall and by histology. The authors utilized the robust Utah Population Database, which includes data on more than 11 million Utah residents to match women with endometriosis to women without endometriosis in a 1:5 ratio. This database utilizes linked vital records, health facility records, the Utah Cancer Registry, and the University of Utah and Intermountain Health records. The exposure—endometriosis—was subclassified as superficial, deep infiltrating, ovarian endometriomas, or other. There were 597 ovarian cancer cases, the outcome of interest. The authors demonstrated an increased risk for ovarian cancer in women with endometriosis compared with those without (adjusted hazard ratio [aHR], 4.20 [95% CI, 3.59-4.91]). This risk was highest with subtypes such as clear cell and endometrioid carcinoma (aHR, 11.15 and 7.96, respectively). Additionally, deep infiltrating carcinoma and/or ovarian endometriomas were associated with the highest ovarian cancer risk (aHR, 9.66 [95% CI, 7.77-12.00]). Figure 2 in this publication clearly demonstrates the statistical significance pertaining to types of endometriosis and histologic subtypes.

Although the authors attempted to control for key confounders, the dataset could not provide detail on medical management of endometriosis, such as oral contraceptives or gonadotropin-releasing hormone agonists. Additionally, there is a possibility that women in the control cohort could have had undiagnosed endometriosis. Moreover, germline or somatic *BRCA* sequence variations or homologous recombinant deficiency (HRD) (*BRCA* wild type) status were not reported or known. A discordance in HRD could certainly modify the risk assessment, particularly for endometrioid and serous histologies. A key contribution of this investigation was the observed associations between subtypes of endometriosis with overall risk for ovarian cancer as well as histologic subtypes of epithelial ovarian cancer, distinguishing this cohort study from previous publications.

However, drawing clinical recommendations from these reported observations, particularly with respect to deep infiltrating endometriosis, would require a clear and consistent definition of deep infiltrating endometriosis in this dataset over the entire study interval from 1992 to 2019 and for the state. The authors do not provide a definition for this subtype of endometriosis except for *International Statistical Classification of Diseases and Related Health Problems* codes. Furthermore, a consensus definition has slowly evolved. Despite this potential challenge, the increased risk associated with deep infiltrating and/or ovarian endometriosis was clearly significant.

The mechanism for malignant transformation of endometriosis has not been clearly elucidated. It may be related to activation of oncogenes, such as *KRAS* and *PI3K*, as well as inactivation of tumor suppressor genes, such as *PTEN* and *ARID1A*.[16,17] More than likely, it is multifactorial: genetic, hormonal, and immunologic. Importantly, there is evidence clearly demonstrating molecular similarities between endometriosis and endometriosis-associated ovarian cancer,[18] further supporting the association and the possibility that endometriosis is a precursor to particular subtypes of epithelial ovarian cancer.

This investigation adds to the data that clearly demonstrate the association of endometriosis and epithelial ovarian cancer, particularly clear cell and endometrioid. This study also provides important new information identifying an increased risk with particular phenotypes of endometriosis, such as deep infiltrating and/or ovarian. It is imperative that future investigations explore the biology of this association and mechanisms contributing to malignant transformation. Moreover, molecular assessment of women with endometriosis and ovarian cancer, compared with women with endometriosis without ovarian cancer, may facilitate the identification of women at higher risk. Ultimately, characterizing these differences could support consideration for a more prescriptive surveillance recommendation or possible strategies for risk reduction. Moreover, these data support the importance of counseling women with deep infiltrating and/or ovarian endometriosis regarding the increased risk for ovarian cancer. Although the absolute number of ovarian cancers is limited, the increased risk is significant. In those women who have completed childbearing or have alternative fertility options, consideration for more definitive surgery should be discussed and considered. As always, shared decision-making is essential given these evolving data.

ARTICLE INFORMATION

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