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Review article

Clinical implication for endometriosis associated with ovarian cancer

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ABSTRACT

We reviewed current literature regarding the association of endometriosis and epithelial ovarian cancer based on epidemiology studies, molecular researches and clinical observations. Our methods include a review of literature research of MEDLINE, PubMed, Cochrane Library of Systematic Reviews and reference search in selected papers. The life time risk of epithelial ovarian cancer in women with endometriosis is low, yet there might be a cluster of individuals who have higher risk of developing epithelial ovarian cancer from endometriosis. Endometriosis associated ovarian cancer (EAOC) is predominant in particular histological subtypes of epithelial ovarian carcinoma and are related to some specific molecular aberrations. Clinical observations showed age as an important variable to the development of EAOC. Rapid growth of tumor and solid components in sonography are key features to detect malignant transformation of endometriosis. Evidence is not clear about prophylactic oophorectomy in preventing EAOC in patients with endometriosis. This review provided rationale data for identifying, monitoring, counseling and management of women with endometriosis who are potentially high risk for malignant transformation.

Introduction

Endometriosis is a common gynecologic disease. The estimated frequency among women of reproductive age is 6–10%,[1] and is particular frequent among women with pelvic pain and infertility.[2] It is characterized by endometrial-like tissue outside the uterus, primarily on the pelvic peritoneum, ovaries, and rectovaginal septum, and in rare cases on the diaphragm, pleura, and pericardium.[2]

Endometriosis occurred concomitantly with ovarian cancer, denoted as endometriosis associated ovarian cancer (EAOC), has been documented since the first description of such a condition by Sampson in 1925.[3] Evidence of malignant transformation of endometriosis was approved by demonstrating direct origin of carcinoma from an endometriotic focus.[3] Multiple pathways could have involved in malignant transformation of endometriosis. Endometriosis shares several molecular characteristics with invasive cancer, such as inflammation, tissue invasion, angiogenesis, dysfunction of immune cells, increased local estrogen production, apoptosis, and pro-survival features.[4] Iron-induced oxidative stress derived from repeated hemorrhage due to menstruation was believed to be the major pathway in the malignant transformation of endometriosis.[5,6]

We reviewed literature research of MEDLINE, PubMed, Cochrane Library of Systematic Reviews and reference search in selected papers that related to malignant transformation of endometriosis, focusing on epidemiology studies, molecular researches and clinical observations in EAOC. The objective of this review is to collect data associated with such disease and for selective patient surveillance and management.

Prevalence of ovarian cancer in women with endometriosis

Many epidemiologic studies supported a link between endometriosis and invasive epithelial ovarian cancer based on high prevalence and incidence of epithelial ovarian cancer and endometriosis. A meta-analysis on 28 studies showed that the standardized incidence ratio (SIR, defined as observed cases/expected cases after adjusted for age) for epithelial ovarian cancer in women with surgical or histological diagnosed endometriosis was 1.43–8.95; and the odds ratio (OR, defined as the ratio of disease odds given exposure status) was 1.34. The prevalence (defined as

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cases/person-time of observation) of epithelial ovarian cancer in women with endometriosis was 2.0–17.0%, and the prevalence of endometriosis in women with epithelial ovarian cancer was 3.4–52.6%.[7] The wide ranges of reported incidence and prevalence of epithelial ovarian cancer in women with endometriosis is due to high heterogeneity in meta-analysis. In addition, different criteria used to diagnose endometriosis could result with great difference in the incidence rate (IR, defined as number of new cases per population at risk in a given time period per 10,000 person-year) of epithelial ovarian cancer in women with endometriosis. In a cohort study from the National Health Insurance Research Database (NHIRD) of Taiwan and the Registry for Catastrophic Illness Patients that included 239,385 women, the reported IR of epithelial ovarian cancer in women with endometriosis were 1.90 in women with recalled endometriosis to 18.70 in women with tissue-proved ovarian endometriosis, as compared to those women without endometriosis (0.77–0.89). Consequently, these IRs contributed to a range of crude hazard ratio (HR, defined as instantaneous risk over the study time period) of epithelial ovarian cancer in women with endometriosis as 2.59–24.04.[8]

Endometriosis associated ovarian cancer (EAOC) does not exist as a homogenous group of malignancies, but as several histological subtypes. Based on recalled self-reported endometriosis, a pooled analysis of 13 case–control studies of ovarian cancer that included 13,226 controls and 7911 women with invasive ovarian cancer showed that endometriosis was highly associated with clear cell (odds ratio, OR 3·05), low-grade serous (OR 2·11), and endometrioid ovarian cancers (OR 2·04).[9] No association was noted between endometriosis and risk of mucinous or high-grade serous ovarian cancer, or borderline tumors of either subtype (serous and mucinous).[9] A study from Danish National Patient Register and Danish Cancer Register that included 45,790 women with endometriosis based on clinical diagnosis of endometriosis also reported that the SIR of EAOC was 1.34; and SIR for endometrioid and clear cell carcinoma were 1.64 and 3.64, respectively.[10] In another meta-analysis on 20 case–control and 15 cohort studies that included 444,255 patients with self-reported and histological endometriosis, the RR of endometrioid carcinoma was 1.759 and the RR of clear cell carcinomas was 2.606 in EAOC, whereas serous carcinoma was less frequent (RR, 0.733); and there was no difference in the risk of mucinous carcinoma between EAOC and non-EAOC (RR, 0.805).[11] In the study of National Health Insurance Research Database (NHIRD) of Taiwan that included 5945 women with surgico-pathological diagnosed endometriosis compared with multivariable-matched 23,780 controls, the IR of epithelial ovarian cancer was 11.64, contributing to HR of 4.48; and the HR in clear cell carcinoma subtypes was 7.36.[12]

All these epidemiological studies observed the close association of endometriosis with particular histological of EAOC, i.e. endometrioid and clear cell carcinoma, especially when the diagnosis of endometriosis was more evidence based, such as through surgical-pathological diagnosis.

Pathogenetic similarities between endometriosis and EAOC

Several gene mutations have been identified concurrently in endometriosis lesions and in the EAOC tumors. Many studies have focused on assessing LOH at 10q23.3 (such as loss of heterozygosity (LOH) and mutations leading to functional inactivation of the PTEN tumor suppressor gene, located on chromosome 10q23.3) and MSI (leading to the functional inactivation of the PTEN gene) in EAOC. Sato et al reported LOH at the 10q23.3 locus in 56.5% of solitary endometrial cysts, 42.1% of endometrioid carcinoma and 27.3% of clear cell carcinoma, suggesting that inactivation of genes at 10q23.3 might be involved in these lesions.[13] Furthermore, Ali-Fehmi et al reported LOH at D10S608 in 4.3% of endometriosis lesions and 23.5% of EAOC.[14] Ali-Fehmi et al also reported MSI in 82.6% of endometriosis, 75% of atypical endometriosis and 53% of epithelial ovarian cancer (in 4 of 5, 80% clear cell carcinomas, 3 of the 7, 42.8% endometrioid carcinomas, and 4 of 8, 50% serous papillary carcinomas).[14] These results highlight that endometriosis and atypical endometriosis might act as precursor lesions that have the potential to progress into EAOC.

Loss of BAF250a expression and ARIDIA mutation were frequently and specifically reported in histological subtypes of endometrioid and clear cell carcinoma of EAOC. BAF250a is encoded by ARID1A and has been believed to confer specificity in regulation of gene expression. By immunohistochemical staining, loss of BAF250a expression was reported in 22% (13/59) of endometrioid carcinomas, 47% (17/36) of clear cell carcinoma, 44% (8/18) of contiguous endometriosis, and 8% (3/66) of benign endometriotic ovarian cysts.[15] By whole transcriptomes sequencing, ARID1A mutations were found in 46% (55/119) of ovarian clear cell carcinomas, 30% (10/33) of endometrioid carcinomas, but none of the serous carcinoma.[16] Both ARID1A mutations and loss of BAF250a expression were identified in the tumor and contiguous atypical endometriosis but not in distant endometriotic lesions.[16] These results suggest the close correlation between ARD1A and BAF250a in the pathogenesis of EAOC.

ARID1A and PIK3CA mutations were particularly important in the clear cell carcinoma subtype of EAOC. Using Whole-genome and targeted deep sequencing, concurrent ARID1A and PIK3CA mutations were found in ovarian clear cell carcinoma and in tumor-adjacent and distant endometriotic lesions, regardless of any cytological atypia.[17] In a study that included 23 clear cell carcinomas with synchronous putative precursor lesions (i.e. endometriosis adjacent to carcinoma, with or without cytological atypia), PIK3CA gene mutations were detected in 43% (10/23) of ovarian clear cell carcinomas and in 90% (9/10) of the coexisting endometriotic epithelium, adjacent to the clear cell carcinoma.[18] Using immunohistochemical analysis, loss of ARID1A and PIK3CA were frequently found in 130 cases of ovarian clear cell carcinoma (56.2% and 45.0%, respectively). Loss of ARID1A was particular frequent (76.9%, 20/26) in clear cell carcinoma with concurrent endometriosis. PIK3CA expression was reported not related to clinical features or survival of clear cell carcinoma. But loss of ARID1A, along with low-level HNF-1β expression, was common in patients at cancer recurrence and was correlated with late-stage and worse survival outcome.[19] Another study that included 35 pure-type (73.9% with endometriosis) and 11 mixed-type clear cell carcinoma (45.5% with endometriosis) showed that both ARID1A and p53 were mutually altered in pure-type clear cell carcinoma by immunohistochemical analysis. Altered expression of p53 in these clear cell carcinomas was associated with significant worse prognosis than that of ARID1A ($P < 0.001$).[20] These studies suggested that PIK3CA gene mutation could be a putative precursor for clear cell carcinoma in EAOC; while ARID1A in associated with other genetic mutation (two-hit hypothesis), is a later event in the malignant transformation of endometriosis that leads to disease.

Endometrioid adenocarcinoma showed a distinct molecular profile from clear cell carcinoma. CTNNB1 encodes b-catenin, which plays a pivotal role in the Wnt/b-catenin signaling pathway. CTNNB1 mutations are highly characteristic of ovarian endometrioid carcinoma as they have not been detected in other types of ovarian carcinoma. Mutations in exon 3 of the β-catenin gene were identified in 60% (21/35) of endometrioid carcinoma. The mutations were also detected in the coexisting non-atypical (52.4%) and atypical (73.3%) endometriosis, and the single-nucleotide substitutions were identical in most cases. In contrast, the mutations were not identified in any of the clear cell carcinomas and their

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