Endometriosis and cancer

Hiroaki Kajiyama⁎, Shiro Suzuki, Masato Yoshihara, Satoshi Tamauchi, Nobuhisa Yoshikawa, Kaoru Niimi, Kiyosumi Shibata, Fumitaka Kikkawa

A Department of Obstetrics and Gynecology, Graduate School of Medicine, Nagoya University, Japan
B Department of Obstetrics and Gynecology, Bantane Hospital, Fujita Health University, Japan

ARTICLE INFO

Keywords:
Endometriosis
Ovarian carcinoma
Atypical endometriosis
Genetic alterations
Oxidative stress

ABSTRACT

Endometriosis, characterized by the presence of extra-uterine endometrium, is a common gynecologic disorder in reproductive-age women. Although the detailed molecular mechanism of etiology remains unelucidated, recent studies have gradually revealed both genetic and epigenetic backgrounds of the development of endometriosis. In clinical practice, endometriosis has been recognized as a precursor lesion of several types of malignancies and endometriosis-associated carcinoma. An imbalance between reactive oxygen species and local antioxidants has been reported to contribute to the development of endometriosis-associated carcinoma as well as the pathophysiology of this disease through a systemic inflammatory response in the peritoneal cavity. This review mainly presents an epidemiology, possible etiology of endometriosis, precursor lesions, molecular features, and the association between the microenvironmental accumulations of oxidative stress in endometriosis-associated ovarian cancer progression.

1. Introduction

Endometriosis is an estrogen-dependent, widespread quality-of-life-threatening condition for young women, with an estimated prevalence of 10% [1]. It is characterized by the presence of extra-uterine endometrial glands [2]. Although the detailed etiology of this disorder remains unelucidated, a conventional hypothesis of retrogradely transported endometriotic lesions is widely believed [3,4]. Although endometriosis is attributable to adhesions and scarring with chronic inflammation, commonly causing dysmenorrhea, dyschezia, and chronic pelvic pain [1], it is basically a benign condition. However, in addition to its similar hallmarks of malignant cells, including invasiveness, adhesiveness, and metastatic potentials [5], recent epidemiologic evidence has suggested that endometriosis may cause malignant tumors [6]. Accordingly, endometriosis has been known as a precursor lesion of several types of epithelial ovarian carcinoma. The principle aim of the current review is to deepen the current knowledge of the epidemiological and biological mechanisms and provide new insights into the causes and/or consequences of endometriosis-associated ovarian carcinoma.

2. Clinical feature of ovarian carcinoma

Epithelial ovarian carcinoma (EOC) is the one of the most lethal cancers among gynecologic malignancies worldwide, with more than 238,700 newly diagnosed cases and 151,900 reported deaths per year [7]. EOC is considered to originate from ovarian surface epithelial/neighboring fallopian tube cells and is also recognized as a so-called “silent killer” because most patients with this tumor are asymptomatic until progressing to an advanced stage. In general, this tumor is common in postmenopausal women [8]. In fact, EOC is a highly heterogeneous tumor type, including serous, mucinous, clear cell, and endometrioid histologies with different molecular backgrounds [9]. Clear cell carcinoma (CCC), pathologically diagnosed if typical clear or hobnail cells are growing in a papillary, solid, or tubulocystic pattern, is a comparatively rare malignancy in Western countries, accounting for approximately less than 5% of all ovarian carcinomas [10]. However, this histological type is very widespread in East Asia, and CCC is the second most frequent EOC tumor in Japan [11,12]. A nationwide survey in Japan displayed an increasing incidence of CCC as a proportion of all EOCs, presently accounting for more than 25% of EOCs [13]. According to prior studies, resistance to platinum-based chemotherapy and subsequent poorer clinical outcomes has been

Abbreviations: EOC, epithelial ovarian carcinoma; EAOC, endometriosis-associated ovarian carcinoma; CCC, clear cell carcinoma; EC, endometrioid carcinoma; AE, atypical endometriosis

⁎ Correspondence to: Truma-cho 65, Showa-ku, Nagoya 466-8550, Japan.
E-mail address: kajiyama@med.nagoya-u.ac.jp (H. Kajiyama).

Received 12 December 2018; Received in revised form 13 December 2018; Accepted 14 December 2018
Available online 15 December 2018
0891-5849/ © 2018 Elsevier Inc. All rights reserved.
3. The epidemiology and clinical hallmark of endometriosis-associated ovarian carcinoma

Prior studies have reported that the incidence of endometriosis in patients with EOC is distributed from 4.2% to 14.5% [22–26]. In addition, based on other epidemiologic analyses, endometriosis enhances the risk of the occurrence of EOC [26–28]. According to a comprehensive review of the frequency of endometriosis-associated ovarian carcinoma (EOC), the most and second most frequent pathological type were CCC (35% in 390 cases) and EC (27% in 648 cases), followed by serous carcinoma (5% in 1372 cases) and mucinous carcinoma (4% in 614 cases) [29]. Thus, CCC and EC were the representative histologies of EAO (Figs. 1 and 2). In general, these types of EOC are frequently diagnosed after menopause and are rare in women of reproductive age. However, given the high prevalence of endometriosis in young women, the occurrence of EOC in this generation is problematic due to its life-threatening impact as well as the possibility of the loss of fertility. Moreover, among women with infertility, the relative risk of EAO increases to 2.7% [30]. According to a recent nationwide population-based cohort study, the incidence rates of ovarian cancer in women with endometriosis ranged from 1.90 in women with recalled endometriosis to 18.70 in women with tissue-proved ovarian endometrioma [31]. According to a pooled analysis of 13 case-control studies, self-reported endometriosis was associated with a significantly higher risk of CCC (136 [20.2%] of 674 cases vs 818 [6.2%] of 13,226 controls, odds ratio 3.05, 95% CI 2.43–3.84) and EC (169 [13.9%] of 1220 cases, odds ratio 2.04, 95% CI 1.67–2.48). Thus, an increased risk of CCC and EC was noted in women with endometriosis [32]. In Japan, Kobayashi et al. demonstrated that the prevalence of EAO was 0.72% [28]. In a cohort of patients undergoing infertility treatment, women with endometriosis had the highest risk of developing ovarian cancer (standard incidence ratio: 2.48; 95% CI 1.3–4.2) compared to the general population of women [33]. Similar results were reported by Stewart et al. (with vs without endometriosis: HR 2.33, 95% CI 1.02–5.35) [34]. Furthermore, in a group of women with endometriosis after the age of 45 years, the nulliparity, postmenopausal status, larger endometrioma size (> 9 cm), endogenous or exogenous hyperestrogenism, and/or cysts with solid compartments were elevated risk indicators of EAO [35].

On the other hand, compared to women with non-endometriosis-associated EOC, those with EOC are clinically characterized as younger and with earlier-stage presentation and more favorable oncologic outcome, suggesting that the biologic behavior of EAO may be different from that of non-endometriosis-associated EOC [36]. Endometriosis is unlikely to be associated with aggressive cancer progression since it represents well-differentiated tissue. Paik et al. investigated the oncologic outcomes of patients with endometriosis-derived CCC or EC using propensity score matching based on the stage, age, lymph node metastasis, CA125 level, and residual status after debulking surgery. In an original cohort, both progression-free and overall survival were significantly better in the EAO groups than in the non-EAO groups. However, the association with endometriosis was not significant in multivariate analysis. Further, after propensity score matching, survival differences between the two groups were not significant. In consequence, Paik et al. concluded that cancer arising from endometriosis was not a significant prognostic factor [37].

4. Atypical endometriosis as a precursor lesion of EAO

Historically, pathologists have recognized atypical endometriosis (AE) with histologically intermediate features between benign and malignant showing large hyperchromatic nuclei, an increased nucleus-to-cytoplasm ratio, and cellular crowding [38,39]. This term corresponds to architecturally complex and cytologically atypical proliferative lesions that resemble atypical hyperplasia/intraepithelial neoplasia arising in the endometrium. These lesions sometimes coexist with endometriosis and more commonly EAO, are alterations in the lining epithelium of endometriotic cysts characterized by varying degrees of cellular stratification and disorganization, inflammation, and cytological atypia (Figs. 3 and 4) [40,41]. Ogawa et al. examined the incidence, histopathological characteristics, proliferation activity of endometriosis, and AE associated with ovarian carcinoma by reviewing microscopic slides of primary lesions from 127 patients with primary ovarian carcinoma. Of the 127 patients, 37 had endometriosis, including 29 cases with atypical endometriosis. This study reported that the transition from typical endometriosis to atypical endometriosis was observed in 22 cases, and the transition from atypical endometriosis to carcinoma in 23 cases, suggesting a precancerous status [42]. On the other hand, according to a larger case series by Fukunaga et al., atypical glandular changes were observed in 1.7% (4 of 255) of ovarian endometriosis patients. However, AE is more frequently observed in 36% (18 of 50) of CCCs and 23% (7 of 31) of ECs [41].

To seek a potential biomarker of cancer risk in patients diagnosed with atypical endometriosis, Stamp et al. immunohistochemically examined 35 cases of EAO and 8 cases of non-cancerous atypical endometriosis. In 35 patients with EAO, BAF250a IHC showed a loss of expression in 14 cases (40%). Atypical endometriosis was present in 10 of these cases, 6 of which showed BAF250a loss (60%). BAF250a loss
was not observed in the 8 cases of non-cancerous atypical endometriosis. Thus, Stamp et al. suggested that BAF250a expression may be a biomarker of cancer risk in patients diagnosed with atypical endometriosis [43]. However, further research is necessary to clarify whether atypical endometriosis exists as a precursor lesion of EAOC or if it reflects only a reactive histological background or inflammation.

5. Molecular features of EAOC

New molecular findings about EAOC have been provided suggesting that these tumors are clinically different entities. EAOC is more likely to show similar hallmarks to type I EOCs, including endometrioid, clear cell, mucinous, and low-grade serous carcinoma, with modest clinical behavior and coexistence with the corresponding precursor lesions. Similar to other type I EOCs, EAOC is believed to arise in a stepwise generation in an adenoma-carcinoma sequence. In general, type I tumors are known to show mutation of K-RAS, PTEN, and β-catenin/Wnt and microsatellite instability [19,36,44]. K-RAS mutations occur significantly more frequently in mucinous and EC tumors, but not in normal or atypical endometriosis bordering the cancerous region. Therefore, K-RAS mutations may be associated with late events in the endometriosis-CCC sequence [45]. DNA analysis revealed that K-RAS mutations were detectable in CCC but not in endometriosis or atypical endometriosis. It is possible that K-RAS mutations are associated with the malignant transformation of atypical endometriosis into endometriosis-associated CCC [46]. Similarly, several studies showed results of the frequency of PTEN mutations in endometriosis [47–49]. In particular, Sato et al. examined 20 ovarian endometrioid carcinomas, 24 clear cell carcinomas, and 34 solitary endometrial cysts of the ovary for LOH at 10q23.3 and point mutations within the entire coding region of the PTEN gene. They found that somatic mutations in the PTEN gene were identified in 4 of 20 ovarian ECs (20.0%), 2 of 24 CCCs (8.3%), and 7 of 34 solitary endometrial cysts (20.6%). These results indicate that reduced expression of PTEN may be involved in the malignant evolution of endometriosis [47] and that inactivation of the PTEN gene is an early event in the development of EAC and CCC [49].

ARID1A is considered a tumor-suppressor gene, and the protein encoded by ARID1A, BAF250a, is a key component of the multi-protein SWI/SNF chromatin remodeling complex present in all eukaryotes [50]. The precise molecular mechanisms related to the malignant transformation of EAOC have not demonstrated that mutations in the ARID1A gene have been noted in ovarian CCC and contiguous atypical endometriosis but not in distant endometriotic lesions. Wiegand et al. reported that ARID1A mutations, recently found in these carcinomas, were identified in 55 of 119 ovarian CCCs (46%), in 10 of 33 ECs (30%), and in none of 76 high-grade serous ovarian carcinomas, suggesting its usefulness for the diagnosis of EAOC [51]. In addition, Jones et al. demonstrated the presence of ARID1A mutations in ovarian cancer. In a total of 42 CCCs, 57% had ARID1A mutations [52]. Using tissue samples from 22 EAOCs (13 ECs and 9 CCCs) from Japanese patients, Ishikawa et al. reported that the frequencies of somatic mutations in ARID1A, p53, POLE, PTEN, PIK3CA, and KRAS were 19/20 (95.0%), 7/19 (36.8%), 9/22 (40.9%), 13/19 (68.4%), 3/19 (15.8%), and 1/9 (11.1%), respectively. They found that the frequency of ARID1A mutations was significantly higher than reported previously [53]. These findings suggest that ARID1A mutations may represent the basis of EAOC carcinogenesis. Nevertheless, the clinical significance of the loss of ARID1A in EAOC remains unelucidated.

On the other hand, type II EOCs consist of high-grade serous and undifferentiated carcinomas that display aggressive behavior in clinical practice and advanced stage at diagnosis. Traditionally, type II EOCs are also believed to be derived from ovarian surface epithelial cells or
inclusion cyst cells. However, recent studies have suggested that serous carcinomas are considered to originate from serous tubal intraepithelial carcinoma [44,54]. These types of tumors are genetically unstable with frequent p53 gene mutations. This mutation is believed to be specific for the pathogenesis of high-grade serous carcinoma. The p53 mutation was observed in approximately 30% of endometriosis coexisting with CCC, whereas no mutations were detected in solitary endometriosis or endometriosis coexisting with EC [55,56]. Although mutant TP53 is not specific for the pathogenesis of CCC, it is plausible that p53 mutations may involve malignant transformation of endometriosis into CCC.

6. Iron-related oxidative stress and EAOC

In general, iron is an indispensable substance involved in oxygen transport and various enzymatic activities in all mammals. However, in reproductive age women, excessive amounts of iron-related substances, including heme, ferritin, hemoglobin, and free iron, accumulated in endometrial lesions through periodical menstrual bleeding and retrograde reflux in the peritoneal cavity. In the peritoneal fluid of patients with endometriosis, higher levels of iron [57], ferritin [58], transferrin [59], and Hb [60] were detected than in those without endometriosis. Yamaguchi et al. also reported that the contents of endometriotic cysts, especially high concentrations of free iron in these cysts, promote carcinogenesis through iron-induced persistent oxidative stress [61]. Furthermore, Alizada et al., recently demonstrated that serum iron level in patients with endometriosis was significantly higher than that in the control group in a case-control study [62]. Moreover, the iron in the peritoneal fluid possibly derives from the lysis of red blood cells that are not effectively cleared by macrophages, which are commonly the main processors in the clearance of red blood cells and apoptotic remnants. In patients with endometriosis, this pathway is either originally defective or peritoneal macrophages become insufficient/unable to deal with the amounts of hemoglobin present in the liquid [63]. Accordingly, excessive oxidative stress generated as a consequence of the imbalance between reactive oxygen species (ROS) production and antioxidant barriers may be implicated in the pathophysiology of atypical endometriosis and subsequent EAOC in the peritoneal cavity [2,64,65].

Iron and its metabolites can play roles in the generation of a wide range of ROS via the Fenton reaction (Fe^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^-), acting as an inducer of DNA damage and subsequent carcinogenesis [66]. In addition, when hemoglobin appears in the extracellular milieu, it is prone to autooxidation and easily oxidized [67]. Hemoglobin oxidation occurs slowly, which is referred to as “autoxidation” [68]. Hemoglobin is oxidized from the ferrous (Fe^{2+}) oxygenated form (oxyHb-Fe^{2+}) to the ferric (Fe^{3+}) mietform (methHb-Fe^{3+}) with generation of the superoxide anion (O_2^-) as an autoxidation as follows: Hb-Fe^{2+}(oxyHb) + O_2 → Hb-Fe^{2+} - O_2 → Hb-Fe^{3+}(metHb) + O_2 [69]. Hemoglobin autooxidation also generates harmful ROS such as hydrogen peroxide (H_2O_2) as by-products [69,70]. In endometriosis, in spite of the fact that free hemoglobin is toxic, endometriotic cells elaborate scavenging factors to keep its intracellular concentration at low levels through antioxidant enzymes, including heme oxygenase-1 which is strongly expressed in ectopic endometrium [58,71]. Probably, the existence of the appropriate amount of ROS appears to be more advantageous for endometriotic cell growth through ability to survive the oxidative action of these derivatives. When the amount of ROS is counterbalanced by cellular defense by antioxidant enzymes, including heme oxyenases and/or cytochrome P450 family, excessive oxidative stress damages the normal cell function, and has a role in cell death. However, an enhanced antioxidation capability or sublethal levels of ROS display cytoprotective properties and can protect endometriotic cells from cell death or apoptosis but lead to accumulation of DNA damage, aneuploidy, genomic instability, and mutations, finally resulting in the promotion of carcinogenesis [69,72,73].

Clinically, Iwabuchi et al. reported that assessing the relative concentrations of hemoglobin (Hb) species in the cyst fluid using a surrogate indicator of the methemoglobin (methHb)/(oxyhemoglobin + metHb) ratio may be a useful indicator of malignant transformation, identifying patients who require surgical attention [74]. Polak et al. reported that higher 8-OHdG and 8-isoprostane concentrations was observed in the peritoneal fluid of patients with advanced-stages endometriosis, compared with patients with other benign ovarian cysts [75]. More specifically, these iron-induced ROS signals can contribute to carcinogenesis by increasing oxidative stress promoting DNA mutagenesis and gene product inactivation, and activating detoxification and antiapoptotic pathways [76]. On the other hand, oxidative stress caused by iron-related substances may be responsible for the local destruction of the peritoneal mesothelium, leading to the subsequent...
adhesion formation of ectopic endometrial and tumor cells. Moreover, the activity of superoxide dismutase, which catalyzes the dismutation of superoxide into hydrogen peroxide and oxygen and plays an important role as an antioxidant, was downregulated in the plasma of women with endometriosis, suggesting decreased antioxidant capacity in those patients [77].

Because of the overgrowth of endometrial tissue and retrograde menstrual flow resulting in high levels of hemoglobin, heme, and iron, increasing levels of oxidative stress may continue iron-related oxidative stress and subsequent peritoneal damage or carcinogenesis of ovarian endometrial lesions (Graphical Abstract). Thus, through the production of harmful free radical species, endometriosis-related iron toxicity may induce the deregulation of cellular processes, cell dysfunction, and apoptosis or necrosis through lipid peroxidation, protein, and DNA damage, probably leading to EAOC.

7. Endometriosis-associated extra-ovarian cancer

There are questions concerning the extent to which endometriosis or its history can be a risk factor for other malignancies. A Swedish nationwide registry survey of 766,556 person years revealed that there was an increased risk of ovarian cancer (standardized incidence rate (SIR) 1.43, 95% CI 1.19–1.71), non-Hodgkin’s lymphoma (SIR 1.24, 95% CI 1.02–1.49), brain tumors (SIR 1.22, 95% CI 1.04–1.41), and endocrine cancer (SIR 1.36, 95% CI 1.15–1.61) compared to the general population. However, there was no significantly increased overall risk of breast (SIR 1.04, 95% CI 0.98–1.09) and endometrial cancer (SIR 1.19, 95% CI 0.96–1.46) [6]. Moreover, an Australian retrospective case-control study of 1399 patients did not show any association between endometriosis and other malignancies, in part, as a result of common molecular risk factors [77]. Kvasnoff et al. reviewed the available epidemiological findings on the associations between endometriosis and other malignancies and reported that patients with endometriosis were at a higher risk of breast cancers, cutaneous melanoma, and ovarian carcinoma [80]. Particularly in breast cancer, medications for this tumor have applied for endometriosis and vice versa, including aromatase inhibitors, selective estrogen receptor modulators and antiprogestins [81]. Actually, positive evidence that women with endometriosis are more vulnerable to later develop breast cancer was demonstrated [81], including 3 case-control studies [82–84], 2 case-cohort studies [85,86], and in only 1 retrospective cohort study [30]. Furthermore, breast cancer and endometriosis share some common environmental and molecular risk backgrounds. The bioinformatics approach by Roy et al. contributed to identify genes associated with endocrine disrupting chemicals affecting the rectum and lymph nodes, Fertil. Steril. 86 (2006) 543–547.


M. Hijashi, H. Kajiyama, K. Shibata, M. Mizuno, K. Mizuno, S. HosoNO, M. Kawai,
H. Kajiyama et al.

Free Radical Biology and Medicine 133 (2019) 186–192


