Endometriosis and Ovarian Cancer: an Integrative Review (Endometriosis and Ovarian Cancer)

Aline Veras Morais Brilhante1*, Kathiane Lustosa Augusto2, Manuela Cavalcante Portela2, Luiz Carlos Gabriele Sucupira1, Luiz Adriano Freitas Oliveira1, Ana Juariana Magalhães Veríssimo Pouchaim1, Lívia Rocha Mesquita Nóbrega1, Thaís Fontes de Magalhães3, Leonardo Robson Pinheiro Sobreira3

Abstract

Despite being initially considered a benign disease, it is widely thought nowadays that endometriosis and especially ovarian endometriomas are neoplastic conditions with the potential to become malignant. This review was conducted to summarize, in a concise and systematic manner, the available scientific data relating endometriosis to ovarian cancer, published in the past five years. After reading abstracts and applying our predefined inclusion and exclusion criteria, a final list of 11 scientific papers was obtained and subjected to review. Endometriosis is associated with an increased risk of developing epithelial ovarian cancer (EOC), mainly of endometrioid and clear cell subtypes. This might be by virtue of the high estrogen concentration with the disease, which leads to malignant proliferation of endometriotic cysts, or be due to mutations in the ARID1A gene and consequent loss of BAF250a expression. The iron produced in the fluid of endometriotic cysts promotes oxidative stress, which in turn may cause genetic mutations and malignant progression of ovarian cysts.

Keywords: Endometriosis- neoplasm- ovarian cancer- review

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Introduction

Endometriosis, defined as the presence of endometrial glands and stroma outside the uterine cavity, is a condition that, in addition to being relatively common, has the potential to cause harm to patient’s health and lifestyle on several levels (Ballard et al., 2008). The main symptoms associated with deeply infiltrating disease are pain (which can be devastating for some patients), and infertility. Common complaints include dysmenorrhea, dyspareunia, chronic pelvic pain, painful bowel movements, tenesmus, urinary dysfunction and low back pain (Andres et al., 2014).

Despite being initially considered a benign disease, the wide opinion nowadays is that endometriosis and especially ovarian endometriomas are neoplastic conditions with the potential to become malignant (Chene et al., 2015). Large studies have demonstrated the presence of ovarian carcinoma in 5 to 10% of cases of endometriosis; while others have shown that malignant transformation through atypical endometriosis, described as glands with atypical cytology or architecture, occurs clinically in 0.7 to 1.6% of patients in a 8-year follow-up (Matsumoto., 2015).

However, there is still controversy around the possibility that endometriosis-associated neoplasms may represent distinct histologic entities (Scarfone et al., 2014). Researching this topic can result in significant clinical and prognostic differences associated with this specific disease subgroup.

With this in mind, this integrative review intended to summon, in a concise and systematic manner, the available scientific data that relate endometriosis to ovarian cancer, published in the past five years.

Material and Methods

Methods

This integrative review aims to synthesize and describe the results of multiple scientific reports, providing straightforward knowledge regarding this topic. To create our bibliographic database, a literature search in the Biblioteca Virtual de Saude (BVS) and PubMed/MEDLINE was performed, using the keywords “endometriosis” and “neoplasm” of the Medical Subject Headings (MeSH) and their Portuguese translation, which

1University of Fortaleza (UNIFOR) Medical School, 1321 Washington Soares Ave, Edson Queiroz, 2Maternity School Assis Chateaubriand (MEAC) in Federal University of Ceará (UFC) and University of Fortaleza (UNIFOR) Medical Schools Fortaleza, 3Federal University of Ceará (UFC), Coronel Nunes de Melo Street, no number, Rodolfo Teófilo, Fortaleza, Ceará, Brazil. *For Correspondence: alineveras@unifor.br
are considered appropriate according to the Descritores em Ciências da Saúde (DeCS) criteria for keywords at BVS.

Clinical trials and observational (cohort, case-control and cross-sectional) studies indexed in the past five years in the above-mentioned databases, which investigated the relationship between endometriosis and ovarian carcinoma, were included. Editorials, opinion articles, letters to the editor and comments were excluded.

Our search yielded 36 articles, 11 of which were duplicates, resulting in a final list comprising 25 papers. They were then analyzed using a validated instrument (URSI, 2005) that allows identification of the reports, characterization of their methods and strictness of the criteria used, all considering the study design (Lobindo-Wood, Haber, 2006) and level of evidence (Melnik, Fineout-Overholt, 2005) for each of them.

After reading the abstracts and applying our predefined inclusion and exclusion criteria, a final list of 11 scientific papers was obtained and resulted in this review. The article selection process is summarized in Figure 1.

Results

Selected reports were analyzed and synthesized in order to gather, in an integrative review, the knowledge published worldwide regarding the association between endometriosis and ovarian neoplasm. Included articles are summarized in Table 1.

Discussion

Epidemiological evidence

Endometriosis is associated with an increased risk of developing epithelial ovarian cancer (EOC). Kumar et al showed that up to 19% of EOC were associated with endometriosis, while Melin et al also reported that younger women with a diagnosis of endometriosis were at increased risk of developing endometriosis-associated ovarian carcinoma (EOAC).

Patients with tissue-proved endometriosis are also at increased risk when compared to women with recalled and/or self-reported endometriosis. This statement is based on the study published by Lee at al., (2015), who described a median interval between cohort index date and EOC occurrence of 1203.5 days for recalled and 14 days for tissue-proved endometriosis; in endometriosis-free women, this interval remained relatively constant, ranging from 3381 to 3469 days.

EOC is commonly detected at earlier stages. According to Acién et al., (2015), patients with EOC are younger, suggesting that perhaps they are an intermediate stage in pathological progression.

An study that examined the magnitude of the risks of ovarian, endometrial, breast and colorectal cancers in women with newly diagnosed endometriosis or adenomyosis found an association between ovarian endometriosis and ovarian cancer (Kok et al., 2015). Nonetheless, many studies have important limitations related to small sample sizes (Buiss et al., 2013) and, because of the inconsistency of data found in the literature, the European Society of Human Reproduction and Embryology recommends that women be informed that there is no evidence that endometriosis increases cancer incidence (Dunselman et al., 2014).

Histologic Subtypes

Ovarian cancer has several histologic subtypes, but the endometrioid and clear cell are likely the most studied of them. Reports by Scarfone et al., (2014), who focused on the endometrioid subtype, suggest that endometriosis-associated endometrioid carcinoma (EAEC) has clinical features that are different from those of non-endometriosis-associated endometrioid carcinoma (NEAEC). Moreover, the research performed by his team, involving both EAEC patients as well as endometriosis-associated clear cell carcinoma (EACCC) cases, suggests that these histologic subtypes should be regarded as two different clinical entities since their only overlapping characteristic is the higher prevalence in younger women, when compared to cases that are not associated with endometriosis.

EAEC is usually identified at earlier stages and has a higher incidence of synchronous endometrial tumors. EACCC, in turn, presents clinically as a pelvic mass with no ascites, and has a better survival rate than tumors that are not associated with endometriosis. This may be due to the fact that women with endometriosis are generally followed more closely by their physicians; this study, however, was not able to perform statistical analysis due to small sample size. Further, another study noticed that 41.4% and 3.8% of endometrioid carcinoma (EC) and clear cell carcinoma (CCC), respectively, presented with synchronous endometrial cancer. This might happen by virtue of the high estrogen concentration in the disease, which leads to the malignant proliferation of endometriotic cysts; or due to mutations in the ARID1A gene and succeeding loss if BAF250a expression. Furthermore, Davis et al., (2014) showed that the presence of primary, asynchronous malignancies were more common in patients with endometriosis-associated cancers.

Nearly 42% of CCC present with loss in BAF250a protein expression. It has also been proposed by Xiao et al that CCC arises from HNF-1β-positive epithelial cells, while EC arises from HNF-1β-negative cells.

Endometriosis-associated carcinoma was shown to more commonly be unilateral, while cases without
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The exact mechanism by which malignant transformation in endometriosis occurs has not yet been demonstrated. However, Xiao et al. reported that loss of BAF250a protein, upregulation in HNF-1β and loss of estrogen receptors are common in atypical endometriosis. The precancerous cell must undergo several alterations in order for a tumor to develop. Such changes may have multiple underlying mechanisms, but one of the most studied refers to oxidative stress, which may be associated with genetic abnormalities.

In EOC, a pathogenic pathway commonly suggested relates to estrogen, considering the mutations seen in β-catenin (present in 60% of endometriosis-associated cases (Matsumoto et al., 2015) and PTEN genes. Fewer estrogen receptors are found in CCC. The iron produced endometriosis were generally bilateral and had ascites. This might be explained by the fact that those not associated with endometriosis grow within a cyst, while those associated with the disease arise from a cyst. Davis et al., (2014) suggested that women with endometriosis-associated cancers would have better prognosis and improved survival rates when compared to patients with cancers not associated with endometriosis due to early diagnosis. However, prognosis and survival rates did not differ between groups, despite patients with non-endometriosis-associated cancers having higher recurrence rates.

Women with EAOC are likely less susceptible to standard chemotherapy regimens with platin/taxane-based regimens (Lowery et al., 2012), with greater resistance rates to platin in patients with CCC (Davis et al., 2014). Therefore, as recommended by MD Anderson, CCC patients are more efficiently treated when radiotherapy is used.

Molecular, genetic and inflammatory mechanisms

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in the fluid of endometriotic cysts promotes oxidative stress, which may cause genetic mutations. Thence, the association of iron-mediated oxidation due to repeated hemorrhages that occur in endometriosis, as well as the down-regulation of estrogen receptors, are suggested as causes for the development of CCC (Scarfone et al., 2010). Along with the regurgitation of endometrial cells from preexisting endometriosis (Kajihara et al., 2012). On the other hand, the endometrioid subtype associated with endometriosis should be caused by Müllerian metaplasia. Against what used to be the common belief, Guo et al. (2014) reported that ovarian cancers (serous, endometrioid and clear cell) derived from the fallopian tubes and endometrium, not from the ovary itself.

Considering that oxidative stress may be associated with genetic alterations, it is reasonable to remark and comment on part of such affected genes. Table 2 shows the genes mentioned in this review and a summary of their physiologic roles. Their relationship to carcinogenesis is cited in Table 2, and is further discussed along the study. In EACC, there is a higher frequency of AID1A mutations than in EC and EAEC. EAEC, in turn, has more frequent mutations in the PTEN, KRas and β-catenin genes. It has been suggested that β-catenin and PIK3CA mutations are related to initial events in EC genesis; mutations in the latter are found in 27.3% of EOC and 36.4% of ovarian CCC, as reported by Matsumoto et al. (2015) in a cross-sectional analysis of 83 women with EC and CCC.

Worley Jr et al. (2015) demonstrated that the ARID1A-encoded protein expression is decreased in ovarian CCC. This group noticed that loss in this gene function is also present in endometriotic lesions located near the primary site of malignancy (contiguous endometriosis), suggesting that ARID1A happens early in tumorigenesis and that, when combined with another genetic mutation (two-hit hypothesis), leads to disease (Chene et al., 2015). ARID1A mutations were found in 41-57% of ovarian CCC, 30-48% of ovarian EC, approximately 40% in contiguous endometriosis, and 15-20% of benign ovarian cyst patients. Chene et al., 2015) also suggested that patients with ARID1A mutations in apparently benign endometriosis should be considered as at risk of further malignant transformation.

Still according to the findings published by Chene et al., 2015), there appears to be an association between ARID1A mutations and loss of BAF250a expression monitored through immunohistochemistry. Loss of this protein function, in addition to alterations in γH2AX, pAKT activation and activation of apoptosis pathways, all seem to be early molecular events in EAOC. Wiegand et al reported that ARID1A mutations and loss of its BAF250a protein is the most frequent molecular event in the development of ovarian CCC and EC. The BAF250a protein, however, is not absolutely related to the ARID1A gene, considering that loss of protein expression has been
reported in around 70% of tumors with mutations in this gene. (Lowery et al., 2012).

Lowery et al., (2012) proposed that ovarian CCC and EC would have different etiologies based on whether or not there is a loss in BAF250a expression, considering the complex role of this protein in chromatin remodeling and regulation of transcription of certain other genes. Chene et al., (2015) demonstrated that loss in BAF250a was present in 22% of EC, 47% of CCC, 44% of contiguous endometriosis and 8% of benign ovarian cysts cases; while Lowery et al., (2012) reported that there were no convincing associations between BAF250a expression and epidemiological risk factors in relation to endometriosis and ovarian cancer.

Early activation of the PI3K/AKT pathway has been found in contiguous endometriosis and in EAOC. Yamamoto et al described somatic mutations in PIK3CA in 40% of CCC and, in this group, over 70% of patients had ARID1A deficiencies. It has also been described that PIK3CA occur at early stages in the development of atypical endometriosis.

Methylation of RUNX3 and loss in its protein expression were more frequent in EAOC than in benign ovarian endometriosis. However, a high percentage of RUNX3 mutations were found in women with benign ovarian endometriosis, thus suggesting that epigenetic changes in precancerous lesions may result in patients carrying abnormal methylation patterns. RUNX3 methylation is an early event in EAOC pathogenesis.

Suzuki et al described that the frequency of RUNX3 promoter methylation was higher in patients with endometriosis than in those without the disease.

Hypermethylation of RUNX3 is closely related to estrogen metabolism, and that this gene’s epigenetic inactivation is vital to the malignant transformation of the endometriotic ovary. Molecular alterations in eutopic endometrial tissue might be the source for malignant transformation of the eutopic endometrium; and both eutopic and eutopic endometrium can be synchronously endometriotic ovarian tissue. Although such marker is more specific for CCC, there were no differences in its expression throughout the different subtypes of ovarian cancer. Its overexpression has been referred to as a late event in tumorigenesis. The ER biomarker, in turn, was downregulated in CCC compared to the normal ovary, to the endometriotic ovary, and to the ovary with other histologic subtypes of cancer. The expression of such marker remained high in endometriotic lesions whether they were located adjacent or distant from the tumor; but was lost in clear cells, suggesting it to be a late biomarker.

Expression of pAkt, γH2AX, BAX and BAX proteins was increased in EAOC and contiguous endometriosis; expression of pATM, pCHK2 and Bel2, on the other hand, was decreased. Pro-apoptotic activation factors such as BAX, BIM and γH2AX are more expressed in contiguous endometriosis than in endometriosis-associated ovarian cancer, and should be regarded as an initial barrier protecting pre-invasive endometriotic lesions from carcinogenesis.

The growth factor TDGF1 was underexpressed in endometriosis and EAOC; its roles are relate to cell transformation and oncogenesis.

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