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REVIEW ARTICLE

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Endometriosis and risk of ovarian cancer

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ABSTRACT

Endometriosis is common in premenopausal women and affects about 10% of women of reproductive age. It is a benign condition but demonstrates malignant behaviour with recurrences and metastases. Its tendency to increase the risk of specific subtypes of ovarian cancer is being discussed, because they exhibit specific clinical features that distinguish them from classical ovarian cancer. Malignant transformation of endometriosis goes through its transition to atypical endometriosis. Although endometriosis-associated ovarian carcinomas have a good prognosis, adequate follow-up and monitoring after treatment of endometriosis are recommended.

Key words: endometriosis, ovarian cancer, endometriosis-associated ovarian carcinoma, rate, prognosis

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Endometriosis (E) is one of the most common diseases in premenopausal women, affecting about 10% of women of reproductive age [1]. It is a chronic disease characterized by endometrium-like tissue, glands, and stroma outside the uterine cavity. It is oestrogen-dependent and most commonly affects the ovaries, fallopian tubes, and the pelvic peritoneum. The disease often has a substantial impact on the quality of life of those affected. Usually, it manifests itself with the following symptoms: dysmenorrhea, dyspareunia, chronic pelvic pain, infertility, urinary or digestive symptoms [2]. The diagnosis can be suspected by ultrasound and MRI tests, but the final diagnosis is based on histopathological examination [3]. Various theories explain the occurrence of endometriosis, the most common being retrograde menstruation, genetic predisposition, lymphatic spread, immune dysfunction, metaplasia, or environmental causes [4, 5]. Although E is considered a benign disease, it increases the risk of ovarian cancer [6–9]. Two main mechanisms are suggested to explain this correlation: (1) both diseases coexist and are the result of shared risk factors and their effects; (2) endometriotic cells gradually transform into cancer cells [1].

Atypical E is considered an intermediate state between E and OC [10]. This leads to the conclusion that E is a precancerous condition. More than 2/3 of endometriosis-related ovarian tumours develop in the presence of atypical E [11]. Some of the risk factors for the development of atypical E are: early age of onset, long duration of disease, obesity, dysmenorrhea, perimenopause and menopause, irregular vaginal bleeding, a gynaecological examination of tumour fixation, tumour diameter over 80 mm, a rapid increase in tumour size, the number of abortions, uterine myoma, thyroid disease, and multiple foci of endometriosis [12].

Endometriosis and OC share some quite similar features such as local invasion, neoangiogenesis, increased expression of vascular endothelial growth factor (VEGF), lymphangiogenesis, resistance to the mechanisms of apoptosis, COX-2 overexpression, and genomic instability.

To determine whether endometriosis is associated with an increased risk of ovarian cancer, 13 extensive epidemiological studies were conducted in North America, Australia, and Europe on 23,000 women (13,326 controls; 7,911 with invasive ovarian carcinoma (OC), and 1,907 with borderline malignancies). The studies established the following results [13]. Women with a history of endometriosis have a significantly higher risk (> 2.5 times) of developing three specific

histotypes of ovarian carcinoma: clear cell carcinoma (atypical endometriosis is the immediate precursor of clear cell carcinoma) [14]; endometrioid carcinoma; low-grade serous carcinoma (LGSCO). Several studies published between 2008 and 2014 validate the term endometriosis-associated ovarian carcinomas (EAOC) [15–19]. EAOC is presented as an ovarian carcinoma with both cancer cells and endometriotic cells observed in the same ovary, cancer presence in one ovary, and endometriosis in the other ovary; or presence of ovarian cancer and pelvic endometriosis [20].

The most important conclusions reached by the authors of these studies are the following:

1. Ovarian endometriosis is a risk factor that can lead to the development of endometrioid and clear cell ovarian carcinomas within 5 years [15].
2. The risk of malignant transformation varies between 2 and 17% according to a meta-analysis [16].
3. Risk factors for EAOC are: ovarian endometrioma ≥ 9 cm, and peri- and post-menopausal patients [17].
4. EAOC patients are 10 years younger (mean age 50 years) than other ovarian cancer patients [18].
5. Hyperoestrogenemia is a risk factor for the development of EAOC [19].

EAOC is presented with some specific clinical features that distinguish it from OC: it affects younger patients, shows lower CA-125 levels, it has a better prognosis and a higher number of clear cells than in ovarian cancer [21].

The relative risk (RR) of developing specific histological subtypes of OC for patients with endometriosis is calculated as follows [16]:

1. clear cell ovarian carcinoma — 3.05;
2. endometrioid ovarian carcinoma — 2.04;
3. low-grade serous ovarian carcinoma — 2.11;
4. high-grade serous ovarian carcinoma — 1.13;
5. mucinous ovarian carcinoma — 1.02.

The most extensive and significant survey reported on this topic is a meta-analysis by Kim et al. (2014) [22], which included 1,625 studies and a contingent of 444,255 patients. The authors compare the EAOC with the non-EAOC and reach the following conclusions:

1. endometriosis increases the risk of OC (RR 1.265).
2. EAOC patients have better prognosis and survival.
3. EAOCs are more common in nulliparous women and are usually in FIGO stage I, II.
4. endometrioid (RR = 1.759) and clear cell (RR = 2.606) histological subtypes are more common in EAOC, while serous carcinomas are less frequent (RR = 0.733).

Specific histological, cellular, and molecular markers have been identified as responsible for the malignant transformation of E and underlie the pathogenesis of EAOC [22]. These are:

1. *KRAS* and *PTEN* genes mutations;
2. *ARID1A* gene mutation — it occurs in 46% of the cases of clear cell ovarian carcinoma (CCOC), and in only 30% of endometrioid ovarian carcinoma (EOC) cases; it is not found in high-grade serous ovarian carcinoma (HGSOC).

These mutations inhibit the expression of the BAF250a protein (a tumour-suppressor gene). They are regarded as markers of malignant transformation underlying the pathogenesis of the EAOC.

There are several stages of malignant transformation: normal endometrium, endometriosis, atypical endometriosis, EAOC. External and internal factors, inflammation, and oxidative stress contribute to the progression from one stage to the next. However, genetic factors and mutations in the genes mentioned above exert the most significant influence. It is assumed that the immune system (macrophages) and endometrioid cells' proliferative activity have an additional role as co-factors [23].

Apart from the indisputable evidence of endometriosis association with ovarian carcinoma, other factors are reducing the risk of ovarian cancer in women with endometriosis. Since 2004, oral contraceptives have been shown to reduce the risk of OC by 50–60% in women with endometriosis [24]. Studies published in 2013 established that unilateral oophorectomy significantly reduces the risk of OC compared to endometriosis patients who underwent conservative nonsurgical treatment. Additionally, the studies reported on the protective effect of childbirth and hysterectomy [25, 26].

The available data considered so far indisputably prove that endometriosis is associated with the development of some OC histological types. An intriguing question is whether there is a link between the location of E and the risk of cancer. The results of Finnish study (data retrieved from the Finnish Hospital Discharge Registry and the Finnish Cancer Registry) were published in 2018 [26]. The study covered the period of 1987 to 2012, and included 49,933 women with surgically verified endometriosis. Depending on the organ localization of endometriosis, the distribution is as follows: ovaries — 23,210 cases; peritoneum — 20,187 cases; deep infiltrating endometriosis (DIE) — 2,372 cases.

The Finnish study shows that patients with endometriosis have a 2.3 times higher risk of developing OC — EAOC are endometrioid and clear cell histological subtypes. In addition to these confirmatory results, the authors make an original contribution by proving that endometriosis patients have a significant risk of developing borderline ovarian tumours (BOT) [27]. Depending on the localization of endometriosis, ovarian cancer risk is highest among women with ovarian endometriosis; peritoneal and DIE do not increase the risk.

After a 10-year follow-up, the authors found that the excess risk of ovarian cancer among women with ovarian endometriosis translates into two excess cases per 1,000 patients.

In conclusion, the following clinical groups are at an increased risk of developing EAOC: patients aged > 45 years; nulliparous patients; diagnosis of endometriosis in postmenopausal women; endometriomas ≥ 9 cm; hyperoestrogenism.

The frequency of EAOC varies between 2 and 17%, and endometrioid and clear cell ovarian carcinomas are the most common. Only ovarian endometriosis (not peritoneal and deep infiltrating endometriosis) is related to the progression of EAOC. Malignant transformation progresses to atypical endometriosis and is most often due to mutations in several genes. Although EAOC has a good prognosis, adequate follow-up and monitoring after treatment of endometriosis are recommended.

Conflict of interest

The authors report no conflicts of interest.

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