Krasa Aleksandra, Kozioł Magdalena, Piecewicz-Szczęsna Halina, Pawlicki Mateusz, Łopuszyńska Anna, Krawiec Paulina, Piekarska Ewa. Endometriosis and an increased risk of malignancies. A literature review. Journal of Education, Health and Sport. 2020;10(9):290-298. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2020.10.09.033
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.09.033
https://zenodo.org/record/4026083

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 20.08.2020. Revised: 25.08.2020. Accepted: 12.09.2020.

Endometriosis and an increased risk of malignancies. A literature review

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ABSTRACT

Introduction: Endometriosis is a common gynaecological disorder associated with pelvic pain and sub-fertility, affecting 7–15% of women of reproductive age. The disease is defined as the presence of endometrial-like tissue outside the uterine cavity, primarily on pelvic organs. The aetiology of endometriosis is still uncertain. The disease rarely causes mortality, however, it may have a significant impact on a patient's quality of life. Moreover, several studies have consistently shown that endometriosis is associated with a higher risk of some types of malignancies.

Results: Endometriosis shares several molecular characteristics with invasive cancer, such as inflammation, tissue invasion, angiogenesis, dysfunction of immune cells and pro-survival features. Studies have shown that ovarian cancer, especially clear cell, endometrioid and serous, has been associated with endometriosis. Furthermore, the risk of cancer of the uterine cervix has shown to be decreased and the results on the risk of the cancers of uterine corpus or breast are inconsistent. Among non-gynecological cancers, melanoma of the skin, non-Hodgkin-lymphoma, brain and thyroid cancers have also been associated with endometriosis.

Conclusions: Research results indicate that women with endometriosis have an increased risk for some types of malignancies, therefore, they should be under strict gynecological control, even many years after menopause. Further research is needed to prove the real risk of different types of malignant tumors among women with endometriosis. In addition, it is necessary to establish periodic examination schedules among these patients in order to prevent certain types of malignancies.

Key words: endometriosis; cancer risk; ovarian cancer; non-gynecological cancers.

Introduction

Endometriosis is defined as the presence of ectopic endometrium, including glands and stroma, in extrauterine locations. Most often lesions are localized on the ovaries, fallopian tubes and tissue around the uterus and ovaries; however, in rare cases it may also occur in other parts of the body. Martius divided the disease into the following types: *endometriosis genitalis interna* (in the myometrium or fallopian tube), *endometriosis genitalis externa* (in other places of the reproductive system) and *endometriosis extragenitalis* (outside the reproductive system). Endometriosis is most commonly observed among women of childbearing age; however, it also may occur among adolescents, as well as after menopause. The main symptoms are pelvic pain, infertility and dyspareunia. The pain usually occurs during menstruation. Less common complaints include urinary or bowel symptoms. About 25% of women have no symptoms [1].

The observation that endometriosis is a cancer precursor has been confirmed by the presence of the same or similar mutations in endometriosis-associated cancers as well as in adjacent endometriosis lesions [2]. Endometriosis shares several molecular features with invasive cancer, such as inflammation, immune cell dysfunction, tissue invasion, angiogenesis, pro-survival traits, apoptosis and increased local estrogen production [3], which appears to be linked to increased aromatase expression and activity [4]. Additionally, resistance to the anti-proliferative and anti-inflammatory effects of progesterone is associated with a shift in estrogen receptor isoform expression resulting in estrogen-mediated inhibition of progesterone receptor expression [5].

Iron-induced oxidative stress derived from repeated hemorrhage due to menstruation is believed to be the major pathway in the malignant transformation of endometriosis. Oxidative stress leads to increased angiogenesis, endometriosis proliferation, and selective iron-mediated DNA damage leading to potential oncogene mutations [6]. Thusly, inflammatory responses with the hormonal dysregulation in endometriotic implants, may drive carcinogenesis.

Description of the state of knowledge

An ovarian cancer

The epidemiological link between endometriosis and ovarian cancer was first identified in 1925 by Sampson [7]. Some studies have suggested that the link might differ between ovarian cancer histotypes. The Ovarian Cancer Association Consortium (OCAC) reported that endometriosis increases the risk of clear cell ovarian cancer by 3-fold, and the risk of low-grade serous and endometrioid subtypes by ~2-fold, but endometriosis was not associated with other histotypes [8]. The risk of ovarian cancer appears especially increased among patients with a long-standing history of untreated ovarian endometriosis [9].

Kurman et al. defined endometriosis as the potential precursor lesion for CCOC (clear cell ovarian cancer) and ENOC (endometrioid ovarian cancer), and cytologically atypical endometriosis (large nuclei that are either hyperchromatic or pale, increased nucleus-to-cytoplasm ratio, cellular crowding) as the direct precursor lesion [10]; whereas Karnezis classified endometriosis as "high risk" and "low risk" depending on the presence of atypical endometriosis, which is intended as an intermediate precursor that associates typical endometriosis and ovarian cancers [11]. Similarly, Kommoss and Gilks maintain that the assumed precursor of ENOC and CCOC is atypical endometriosis resulting from ovarian implantation of endometrial tissue after trans-tubal spread [12]. Thereupon, cytologically atypical ovarian endometriosis should be considered as a direct precursor of CCOC and ENOC, as atypical endometriosis has been identified contiguous with these tumor histotypes [9].

Furthermore, similar molecular changes have been detected in the nearby endometriosis as in the cancer (ARID1A, PTEN, HNF1B, PIK3CA, K-ras mutations) [13]. Inactivating ARID1A mutations are the most common molecular genetic alteration reported in CCOC and ENOC, but a higher frequency of ARID1A mutations has been detected in CCOC (46–57%) compared with ENOC (30%) [14]. These mutations result in loss of expression of the protein encoded by ARID1A (BAF250a), which normally suppresses cellular proliferation through a p53-dependent transcription regulation of several tumor suppressors including CDKN1A and SMAD3 [15]. Loss of protein expression of the ARID1A tumor suppressor gene has been demonstrated in endometriosis adjacent to clear cell tumor samples [16]. Overexpression of the transcription factor HNF-1beta and PIK3CA mutations are also common in CCOC. Importantly, aberrant expression of ARID1A, PIK3CA, and NF-kB genes has been recognized as the major target genes involved in oxidative stress-induced carcinogenesis, and in the context of the malignant transformation of endometriosis, the high oxidative potential of iron has been emphasized [17]. Furthermore, Yi Lu et al. investigated the shared genetics between endometriosis and ovarian cancer, stratified by ovarian cancer histotypes. They found widespread shared genetics between endometriosis and most EOC (epithelial ovarian cancers) histotypes.

Using two statistically complementary genetic methods - GREML and GRP, strong genetic correlations between endometriosis and clear cell ovarian cancer and endometrioid ovarian cancer and moderate genetic correlation between endometriosis and serous ovarian cancer were demonstrated; with clear cell carcinoma showing the strongest genetic correlation with endometriosis. However, there was no evidence of a genetic correlation between endometriosis and the mucous type of ovarian cancer [18].

An epidemiological link between epithelial ovarian cancer and endometriosis means that women with ovarian cancer are more likely to have a history of endometriosis compared to the general female population.

A cervical cancer and endometrial cancer

The available epidemiological evidence suggests that women with endometriosis are at a decreased risk of cervical cancer. Saavalainen et al. found a strongly decreased risk of cervical cancer of squamous cell histology among women with endometriosis, especially with peritoneal endometriosis [13]. Because the main cause of a cervical cancer is human papillomavirus, one explanation might be the reduced sexual activity, for example, as a result of pelvic pain, and thus lower exposure to the viruses [19]. A. Melin et al. also suggest that women with endometriosis have a decreased risk of cervical cancer. They claim that the reason might be strict gynecological control and more frequent visits to a gynecologist, and therefore regular gynecological and cytological tests. However, the risk of cancer in situ was also reduced, suggesting that these women in fact have a decreased risk of cervical cancer [20].

The risk of the endometrial cancer in women which endometriosis is unclear. Some studies have found no association. For example, Elizabeth M. Poole et al. suggest in their study that endometriosis is not strongly linked to endometrial cancer risk [21]. Moreover, Ingrid J. Rowlands et al. carried out a study on the relation between gynecological conditions such as uterine fibroids, endometriosis, pelvic inflammatory disease and urethra / uterine infections, and the risk of endometrial cancer. The clinical study involved 1399 women with endometrial cancer diagnosed in 2005–2007 and 1539 women in the control group. No relationship was found between endometrial cancer and endometriosis. [22]. Nevertheless, other studies have found an excess risk of endometrial cancer. For instance, Julie Brøchner Mogensen et al., as the first cohort study to date, observed a significantly increased risk for endometrial cancer in women with a diagnosis of endometriosis. 45,790 women with a clinical diagnosis of endometriosis in 1977–2012 were identified in the Danish National Register of Patients. The cohort was connected to the Danish Cancer Register and standard incidence rates were calculated. It was noted that endometriosis was associated with an increased risk of endometrial cancer, mainly type 1 [23].

Due to divergence in research, more studies is needed to establish the link between endometriosis and endometrial cancer.

A breast cancer

Data on the association between endometriosis and breast cancer are inconsistent. While most studies suggest a moderately positive association between endometriosis and the risk of breast cancer, there are also studies that have observed no clear connection and several studies that reported an inverse association [24]. The relation between these two diseases is complex.

Both endometriosis and breast cancer are associated with an abnormal hormonal environment high in estrogen [4]. Moreover, women with endometriosis have an increased inflammation, which may also be associated with breast cancer [25]. In addition, many treatments for endometriosis, including the use of oral contraceptives [26] and nonsteroidal anti-inflammatory drugs, may also alter the risk of breast cancer [27].

Farland et al. investigated the association between laparoscopically confirmed endometriosis and the risk of breast cancer depending on the hormone receptor. Their prospective cohort study included 116 430 women from the Nurses' Health Study II cohort followed from 1989 until 2013. At first, 5389 (5%) women reported laparoscopically confirmed endometriosis. 4979 (3%) breast cancer cases were diagnosed during 24 years of follow-up. Women with endometriosis were not at higher risk for overall, premenopausal or postmenopausal breast cancer, albeit associations varied by hormone receptor status of the cancer. Farland et al. observed that women with endometriosis were not at increased risk of estrogen and progesterone receptor-positive (ER+/PR+) tumors or estrogen and progesterone receptor-negative (ER−/PR−) tumors. However, women with endometriosis had an increased risk for ER+/PR− breast cancer. The increased ER+/PR- breast cancer risk among women with endometriosis should be studied further [28].

Non-gynecological cancers

The association between endometriosis and non-gynecological cancers has not been sufficiently studied. There are several studies indicating an increased risk of melanoma of the skin, non-Hodgkin-lymphoma, brain, thyroid and kidney cancers in women with endometriosis. However, in most of these studies, the causes of the association between endometriosis and these types of cancers are unclear.

Marina Kvaskoff et al. suggest a significant increased risk of skin melanoma in women with a personal history of endometriosis. It is thought that melanoma is associated with female hormone levels, like endometriosis, which is why hormonal hypothesis can explain the relationship between two diseases. Another hypothesis is that endometriosis and melanoma can have common genetic etiological aspects. Endometriosis is associated with molecular genetic alterations in some tumor suppressor genes that have also been shown to be involved in melanoma [29]. Leslie V. Farland et al. investigated the association not only between endometriosis and melanoma but also the association between endometriosis and non-melanoma skin cancers. The study included 98 995 French women aged 40-65 years in 1990. Data on surgically confirmed endometriosis and skin cancer diagnoses were collected every 2-3 years through self-report, with skin cancer cases confirmed through pathology reports. Between 1990 and 2008, 535 melanoma, 247 squamous-cell carcinoma (SCC), and 1712 basal-cell carcinoma (BCC) cases were diagnosed. Endometriosis was associated with an increased overall risk of skin cancer. When considering skin cancer type, endometriosis was associated with melanoma risk but not with SCC or BCC. Therefore, Leslie V. Farland et al. confirm the association between endometriosis and the risk of skin cancer and suggest that this association is the strongest in melanoma [30].

Another neoplastic disease that may be at increased risk among patients with endometriosis is non-Hodgkin's lymphoma (NHL). Janet E. Olson et al. suggest that endometriosis is significantly associated with the risk of NHL. In their study, women who reported endometriosis were 3.2 times more likely to develop diffuse NHL than women without endometriosis. Furthermore, the risk was particularly increased for diffuse NHL and extranodal disease [31].

A. Melin et al. also indicate an association between endometriosis and an increased risk of lymphoma. In their study, women discharged from a hospital, with a diagnosis of endometriosis from 1969 to 2000, were identified using the National Swedish Inpatient Register. Data were linked to the National Swedish Cancer Register to identify cases of cancer. The study showed an increased risk of non-Hodgkin's lymphoma in patients with endometriosis [20]. The association between endometriosis and NHL found in these studies may be linked to abnormal cellular and humoral immune function reported in patients with endometriosis. Generalized polyclonal B-cell autoimmune activation and secretion of immune proteins have been observed in endometriosis. Therefore, there may be an association between B cell activation in endometriosis and the development of B cell lymphomas. Patients with endometriosis have been also reported to have increased numbers of peritoneal macrophages and lymphocytes T and higher secretion of cytokines and growth factors. Additionally, abnormalities in levels of interleukin-6, tumor necrosis factors, and vascular endothelial growth factor may be also observed in patients with endometriosis [32]. Another explanation for the association between endometriosis and NHL may be the increased risk of immunosuppression caused by drugs prescribed to treat endometriosis. Bruce A Lessey indicates that danazol has immunosuppressive properties, including inhibition of lymphocyte proliferation in vitro and suppression of autoantibody production, which may increase the risk of developing lymphoma [33]. Moreover, types of NHL found to be most strongly associated with endometriosis - diffuse and extranodal NHL, are the types of NHL commonly associated with immunosuppression [31].

Studies have shown that women with endometriosis may also have an increased risk of thyroid cancer. Liisu Saavalainen et al. assessed the association of surgically verified endometriosis and risk of non-gynecological cancers according to the type of endometriosis (i.e., ovarian, peritoneal and deep infiltrating endometriosis). All diagnoses of endometriosis were identified from the Finnish Hospital Discharge Register 1987–2012. Non-gynecological cancers diagnosed after the endometriosis diagnosis were obtained from the Finnish Cancer Registry. The cohort of 49 933 women with surgically verified endometriosis and the sub-cohorts of ovarian, peritoneal and deep infiltrating endometriosis were analyzed separately. Liisu Saavalainen et al. found an increased risk of thyroid cancer in the entire cohort and in the sub-cohorts of ovarian and peritoneal endometriosis. That was especially seen for thyroid cancer with papillary histology [34].

Rates of thyroid cancer in women are estimated to be three times that of men which may be linked to female sex hormones . Moreover, the association between estrogens and thyroid cancer have been reported. Some studies suggest that estrogen-mediated modification may play a crucial role in the promotion and progression of thyroid cancer similarly to other estrogen-mediated cancers, such as breast cancer. Muhammad Zahid et al. investigated that unbalanced estrogen metabolism and alterations in potentially carcinogenic estrogen-DNA adducts are observed in women with thyroid cancer. Therefore, estrogen hormonal disorders can be a risk factor for both thyroid cancer and endometriosis [35].

Some studies also indicate an increased risk of brain tumors in women with endometriosis. Melin et al. in a study on cancer risk among women with endometriosis, which included 63 630 women discharged from the hospital diagnosed with endometriosis from 1969 to 2002, showed an increased risk of brain tumors [36]. Moreover, Elizabeth B. Claus et al. in a study assessing the risk of meningioma suggested endometriosis as a risk factor for this brain tumor.

The study included 1124 patients with meningioma (age range 20-79 years) and 1000 people in the control group in the period from May 2006 to February 2010. Patients with meningioma more often than in the control group had diseases associated with hormonal abnormalities, i.e. uterine tumors, breast cancer and endometriosis. The role of hormones (and therefore also endometriosis) in the risk of meningioma is intriguing, but requires further research [37].

Conclusions

The results of the research indicate show that women with endometriosis have an increased risk for some types of malignancies, therefore, they should be under strict gynecological control, even many years after menopause. Further research is needed to establish the relation between endometriosis and the development of malignancies, which will affect the observation and treatment of endangered patients with endometriosis in the future.

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