Relationship Between Endometriosis and Cancer

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1. Definition and Epidemiology of Endometriosis

Endometriosis is a chronic disease characterized by the presence of the endometrial layer outside the uterine cavity.[1] It is an important public health issue that can cause symptoms such as chronic pelvic pain, dyspareunia, dysuria, dyschezia and infertility; depending on the localization.[2] The estimated prevalence of endometriosis is 7-15% in reproductive age and can go up to 50% in patients who have fertility problems.[2] Although the onset of the disease is generally in the early stages of reproductive ages (before 30 years of age), it has the highest incidence in women aged between 35-44 years, due to delays in diagnosis (mean 4-7 years).[2]

Endometriosis is a serious public health problem that can cause chronic pelvic pain, dyspareunia, dysuria, dyschezia, and infertility.

Various theories have been proposed in the etiology of endometriosis. The most convincing one is that the implantation of endometrial cells on the ovary, peritoneum or other pelvic organs caused by the reflux of the endometrial tissue during menstruation from the fallopian tubes..[2, 3]

Early menarche[4-6], short menstrual cycle[7], alcohol use[8] and caffeine consumption[9], which can cause increased amount of estradiol and estrone in the circulation that stimulates ectopic and eutopic endometrial tissue, were associated with increased risk; while parity[10], and oral contraceptive use [11, 12] were associated with decreased risk for endometriosis that is seen during the reproductive period.

There are conflicting results in the literature regarding the relationship between the use of combined oral contraceptives (COCs) and the risk of endometriosis. [13,14] However, the general view of the relationship in between is that, especially for the treatment of pain, endometriotic foci suppressed by the use of COCs may reappear after discontinuation of medication.

Although the relationship between smoking and endometriosis is not yet clear, it is thought that smoking can reduce the growth of endometriotic foci by reducing estrogens in the circulation.[15] However, in a recent meta-analysis published by Bravive et al, there was no relationship found between history of smoking or amount of daily cigarette consumption and endometriosis. [16]

Furthermore, it is thought that lifestyle and eating habits may play an important role in the development of endometriosis, due to its effects on tumor necrosis factor alpha (TNFα), interleukin 6

and other inflammatory cytokines. Particularly in a recent study; dioxins, polychlorobiphenyls and some pesticides, which are organic pollutants, have been reported to be found on an increased rate in the omental and parietal fatty tissues of endometriosis patients.[17] The relationship between physical activity and endometriosis is not yet clear, thus long-chain omega 3 fatty acid consumption has been found to be associated with a reduced risk of endometriosis.[18]

Although it is accepted as a benign disease, endometriosis and especially ovarian endometriomas have been considered to have malignant potential in recent years. As a result of large-scale studies, the incidence of ovarian carcinomas on the basis of endometriosis was reported to be around 2%.[19]

Kumar et al. showed that approximately 19% of epithelial ovarian cancers were associated with endometriosis.[20] Melin et al. also reported an increased risk of endometriosis-related ovarian carcinoma in young women with endometriosis. [21]

The incidence of ovarian carcinoma related to endometriosis is around 2%.

It has been shown that endometriosis-related carcinomas are more likely to be unilateral while carcinomas that are not associated with endometriosis are more likely to be bilateral and co-occurrence with ascites.[21] This situation can be explained by the fact that endometriosis-related carcinomas originate from the cyst itself and that non-endometriosis-related carcinomas form de novo within the cyst.

2. Mechanisms in Ovarian Cancers Associated with Endometriosis

2.1. Molecular, Immune and Genetic Mechanisms

Endometriosis is acknowledged as a benign disease, it has shown a similar to malignant tumors characteristics; such as uncontrolled growth, neo-angiogenesis, local invasion and distant spread trait etc[22].There are many studies on endometriosis-related cancers and their molecular and immune mechanisms.

Cancer cells typically show genomic instability[23]. Most of neoplasms are monoclonal, and many studies have shown monoclonality in endometriosis as well [24,25]. Recently, several molecular pathways have been proposed to explain the transformation from endometriosis to a typical endometriosis and malignancy. Furthermore, many studies present that genetic and epigenetic changes play a role in the pathogenesis of ovarian cancer which associated with endometriosis. According to some studies, 50% of endometriosis lesions ovarian tumor pathogenesis (KRAS, PTEN, B-catenin /

Wnt) contains genes in chromosomal regions somatic genetic changes specifically in endometrioid histological subtype[26-28]. Otherwise, missing of BAF250 protein, increase in HNF-1β and loss of estrogen receptors have been reported to be prevalent in a typical endometriosis. [29]

Ovarian tumors are associated with endometriosis more similar to type 1 epithelial ovarian cancers, but also, they are related with histopathologic types of endometrioid, clear cell, mucinous, and low-grade serous carcinoma. [30]

Somatic genetic alterations in chromosomal regions containing 50 % of endometriosis lesions genes in ovarian tumor pathogenesis (K-RAS, PTEN, B-catenin / Wnt) are resulted particularly in the endometriosis histological sub type. BAF250a protein damage, increase in HNF-1β and diminishing of estrogen receptors are common in a typical endometriosis.

i) Heterozygosity Loss:

It is associated with the tumor suppressor genes revealed in endometriosis inactivation. Phosphatase and Tensin Homolog (PTEN) gene inactivation due to loss of heterozygosity might be initiated the transformation of endometriosis-related ovarian cancer at early stage [31].

ii) PTEN and K-ras: PTEN gene inactivation may play a part in the early malign transformation of endometriosis. [23]

PTEN gene inactivation is observed in clear cell and endometrioid ovarian carcinomas, whereas K-ras mutation is particularly enroll malignant transformation of clear cell carcinoma.

PTEN mutation was shown in 8% of clear cell ovarian carcinomas and in 20% of endometrioid ovarian carcinomas[32]. Dinulesco et al. described that in a rat model where endometrial morphology was observed by stimulated PTEN deletion and K-Ras expression in the ovarian surface epithelium, that suggest a relationship between endometriosis and malignant transformation with these genetic changes[33].

It has also been revealed that K-Ras mutation is not observed in normal endometriosis and atypical endometriosis but noticed in malignant transformation of clear cell carcinoma. [27, 34]

iii) Tumor suppressor p53: Tumor protein 53 (p53) a tumor suppressor gene product, which acts as a transcription factor that regulates cell cycle, function missing, or mutation is a critical problem on development of ovarian cancer. [35] p53 chromosome loss has also been demonstrated severe /late stage of endometriosis. [36]

Type II epithelial ovarian tumors are composed of high-grade serous carcinomas may be related with P53 tumor suppressor gene mutations. While p53 mutation was recognized in 30% of endometriosis-related clear cell ovarian cancers, this mutation is not detected in endometriosis related endometrioid type ovarian cancer and endometriosis [37].

p53 chromosome failure has been determined in severe /late stage endometriosis.
High grade serous carcinomas seen in Type II epithelial could be accompanied by P53 tumour suppressor mutations.

iv) AT-rich interactive domain-containing protein 1A (ARID 1A): ARID 1A is a tumor suppressor gene which encodes BAF250a protein involved in restructuring of chromatins with eukaryotic genome.

This complex is named as one of the accessory subunits of the SWI–SNF remodelling complex that is responsible for cell proliferation, differentiation, tumour suppression and DNA repair process.[23]

ARID1A gene mutation and loss of expression of the BAF250a protein have been found a useful marker for malignant transformation of atypical endometriosis [38, 39]. However, there is still no conclusive evidence about atypical endometriosis histopathologic correlation based on precursor lesion or inflammation.

In case of mutation in ARID1A gene, repair or replication mistakes of damaged DNA may develop and carcinogenesis could accelerate as well. Wiegand et al. reported that, ARID1A expression is lost in 86% of all atypical endometriosis and non-atypical endometriosis. Furthermore, ARID 1A mutation has been shown in both clear cell and endometriosis related endometrioid type ovarian cancer. [40]

BAF250a encoded by ARID1A expression loss might be a potentially useful marker to identify the initiation of malignant transformation of atypical endometriosis.

v) Other Genetic Mechanisms: β-catenin and Wnt/β-catenin pathway mutations are recognized in endometrioid adenocarcinoma.[40-41] There are often functional mutations appeared particularly in PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) and PTEN genes.

However, high-grade endometrioid carcinomas include TP53 mutations, whereas CTNNB1, PIK3CA and PTEN mutations are absent [42]. Early activation of the PI3K / ACT pathway is found in endometriosis and endometriosis- associated ovarian carcinomas. 40% of clear cell carcinomas have been reported with PIK3CA somatic mutation while 70% ARID1A deficiency has been reported in those [43].

It has also been described that PIK3CA is mutated in the early stages of atypical endometriosis.[44] Besides, it has been reported that RUNX3 promoter methylation is at a higher frequency in patients with endometriosis than that is in control patients and higher levels are in endometriosis-related ovarian carcinoma rather than that is in benign ovarian endometriosis. RUNX3 methylation develops early period in the pathogenesis of endometriosis-related ovarian carcinoma [44].

Early activation of the PI3K / ACT pathway was associated with EOC.

eEF1A2, PTCH2, PPP1R1AB and XRCC5 genes were found to be more common at ovarian clear cell carcinoma related endometriosis cases compared to non-cancer related endometriosis cases. SPINTI, Keratin 8, FoxM1B, FOLR1, CRABP1 and Claudin-7 genes in endometriosis-related ovarian carcinoma and ovarian cancers were more common than endometriosis or benign ovarian lesions, while the StAR gene is seen less. In addition, hMLH1 methylation rates have been reported at a higher rate in ovarian carcinoma associated with endometriosis than the benign ovarian endometriosis.

Proapoptotic activation factors BAX, BIM and γH2AX was found to be higher in endometriosis than endometriosis related cancer. This can be considered as a barrier to prevent preinvasive endometriotic lesions from carcinogenesis.

vi) Estrogens:

It has been associated with the development of many cancers especially breast, ovary and endometrium cancers. Increased estrogen levels stimulate proliferation in endometrial cells. This may be involved in malignant transformation of endometriotic cysts. The aromatase enzyme, which converts androgens to estrogen, is not present in normal endometrial tissue, although high concentrations are shown in endometriotic foci. In addition, 17-beta hydroxysteroid dehydrogenase

type 2 enzyme which is found in the normal endometrium and inactivates estradiol by converting it to estrone is not found in endometriotic foci, whereas 17-beta hydroxysteroid dehydrogenase type 1 enzyme which converts the estrone to estradiol, which is a more potent estrogen than estron, is found in endometriotic foci. In addition, estradiol increases Prostaglandin E2 by stimulating the cyclooxygenase 2 enzyme. In the study by O'Donnel et al. carcinogenic effects of estrogens in ovarian cancer are reported to be via estrogen receptor (ER) alpha.[53] It has been shown that levels of both ER alpha and ER beta are increased in active foci compared to inactive endometriotic foci.

The enzyme 17-beta hydroxysteroid dehydrogenase type 1, which converts from estrogen to estradiol, is found in endometriotic foci.

Hepatic nuclear factor beta, VEGF (vascular endothelial growth factor), PDGF (platelet derived growth factor) levels have also been shown to increase in clear cell ovarian cancer and endometriosis-related endometrioid ovarian cancer.[55]

In conclusion, although there are many studies on the possibility of endometriotic tissue harboring mutations in critical genes in the stages up to the development of carcinogenesis, the actual frequency and importance of these genetic mutations are not fully known. ARID1A, K-RAS, PTEN, B-catenin / Wnt and microsatellite instability are believed to play an important role in endometriosis-related ovarian cancer progression. Although ARID1A mutations are thought to be the basis of endometriosis-related carcinogenesis, its clinical significance is still unknown.

3. Risk Factors in Ovarian Cancers Associated with Endometriosis

Although endometriosis is considered to be a benign disease, it is associated with some features of malignant tumors such as tissue invasion, abnormal growth pattern, increased angiogenesis and decreased apoptosis.[56]

Besides, atypical cells detected in many malignant tissues have been reported to be the primary precursor cellular changes for endometriosis-related epithelial ovarian cancer (EOC).57 The incidence of atypical endometriosis (AE) cells in endometriosis-related EOC varies between 20-80%. This great variability of incidence is due to the lack of consensus in the pathological diagnosis of AE. [57]

Various risk factors have been accused in EOC developing based on endometriosis.[58-60] These factors include increased estrogenic activity, resistance to the anti-proliferative effects of progesterone, increased levels of iron as a consequence of tissue oxidative mechanisms resulting with somatic mutations. It is also thought that selective DNA damage may occur due to increased angiogenesis and iron levels as a result of increased tissue oxidative stress.[61]

Although endometriosis is defined as a benign disease, it could present similar features to malignant tumors. In particular, atypical cells are thought to play a role in endometriosis-associated EOC.

In particular, an estrogen-rich and progesterone-poor microenvironment has been reported to increase the risk of endometrioid type carcinoma 35 while iron-dependent oxidative stress is associated with clear cell type of ovarian cancer. [61]

In addition to the aforementioned molecular mechanisms, it is also claimed that some of the clinical parameters are also associated with increased risk of EOC. The risk of endometriosis-associated EOC is thought to increase with advanced age. [62] In particular, when women under 30 years of age have been accepted as a reference, it is reported that women with endometriosis over 50 years of age have a 4.97-fold increase in the risk of EOC.[63] Also, studies reporting that endometrioma size has also an effect on the development of EOCs. [63]Furthermore, if the endometrioma diameter is 9 cm or above, an increased risk of EOC has been reported. [63]

Advanced age and size (> 9cm) might increase risk in endometriosis-associated EOC, while endometriosis surgery reduces this risk. The effect of exogenous estrogen is contradictory.

Some studies investigating the relationship between endometriosis-associated EOC risk and hormone use have reported that exogenous or endogenous estrogen use may increase the risk of EOC. [64] Also, obesity or unopposed estrogen use after hysterectomy is thought to be associated with the increased risk of EOC. [65] In contrast, oral contraceptives used in the treatment of endometriosis symptoms is known to reduce the risk of EOC. In particular, combined oral contraceptives use for over 10 years, might reduce the risk of EOC in women with endometriosis. [66, 67] Although, the relationship between the use of gestagens or GnRH agonists usage and EOC it is not clear due to the insufficient

number of patients, in the studies with the use of Danazol has been proposed to increase the risk of EOK. [68]

There are several opinions related to the course of endometriosis-associated EOC risk after endometriosis surgery. In a study, it is reported that performing a unilateral oophorectomy or removal of all visible endometriotic foci where ovaries are not affected is associated with reduced risk of EOC.[69]

In another study, even if the other ovary was left in place when the other affected one is extirpated, the risk is reported to be reduced. This is specifically explained by the reduction of AE cell load and inflammatory process. [70, 71] However, there is no evidence about adding hysterectomy in the presence of endometrioma reduces the risk of EOC. This could be interpreted that the risk of EOC is already increased when endometrioma is detected and that adding a hysterectomy will not reduce this risk. [69]

In conclusion, advanced age, increased mass size, and estrogenic activity, increased oxidative radicals are accused in the development of EOC associated with endometriosis. It is also reported that these risks can be minimized by surgical removal of endometriotic foci.

4. Types of Ovarian Cancer Associated with Endometriosis

Epidemiological studies have demonstrated that endometriosis is associated with specific subtypes of ovarian carcinoma, particularly with clear cell and endometrioid carcinoma.[72-74] It is now widely accepted in the literature that endometriosis is a direct precursor to the two specific ovarian carcinomas above.

In a pooled analysis of case-control studies, the relationship between ovarian cancers and self-reported endometriosis was investigated in 13 case control series. According to the results of the analysis, the self-reported endometriosis group had significantly higher incidence of clear cell ovarian carcinoma, low-grade serous carcinoma, and endometrioid-invasive ovarian carcinoma compared to the control group.[75] There was no association found between endometriosis and mucinous ovarian carcinoma, high-grade serous carcinoma, or borderline tumors.[18]

Clear cell ovarian carcinoma, low grade serous carcinoma and endometrioid invasive ovarian carcinoma are more common in endometriosis patients.

Scarfone et al. focused on endometrioid subtype of ovarian carcinoma in their study. They reported that endometrioid carcinoma that is associated with endometriosis and endometrioid carcinoma that is not associated with endometriosis have different clinical features. In addition, the researchers in this study included patients with both endometriosis-related endometrioid carcinoma and endometriosis-related clear cell carcinoma and consequently suggested that, unlike the cases that are not associated with endometriosis, different histologic subtypes should be considered as two different clinical entities, with the exception of higher prevalence in young women.[76]

Endometriosis-associated endometrioid carcinomas are usually diagnosed at an earlier stage and are related with a high rate of concurrent endometrial tumors. In endometriosis-associated clear cell tumors, patients usually have a clinical presentation with a pelvic mass without ascites, and a better survival rates than cancers without an association with endometriosis. The reason may be the more frequent follow-up of patients who have endometriosis, but due to the small sample size, it was not possible to generalize the results. In another study, 41.4% of endometrioid carcinomas and 3.8% of clear cell carcinomas were diagnosed with synchronous endometrial cancer. This may be due to the high amount of estrogen in the disease, causing malignant proliferation of endometriotic cysts or mutations in the ARID1A gene and loss of BAF250a expression. In addition, primary, asynchronous tumors are more common in endometriosis-related cancers.[77]

BAF250a protein expression loss is seen in almost 42% of clear cell carcinomas. In a study, it was reported that clear cell carcinoma originates from HNF-1β-positive epithelial cells and endometrioid carcinoma originates from HNF-1β-negative cells.[78]

In conclusion, endometriosis is associated with an increased risk of epithelial ovarian cancer, particularly endometrioid and clear cell subtypes.

High estrogen concentration, ARID1A gene mutation and increased oxidative stress due to iron are associated with EOC in endometriosis.

5. Biomarkers in Endometriosis and Ovarian Cancers Associated with Endometriosis

The diagnosis of endometriosis may be delayed due to the variability of the signs and symptoms of the disease. Currently, there are no reliable biomarkers that can be used in the diagnosis of the disease. Although it is accepted as a benign disease, it is not possible to distinguish it from possible malignancies resulting referral of patients to oncology centers might cause increased anxiety and

possible unnecessary radical surgeries could lead to loss of fertility. [79] Currently, the only reliable method for the diagnosis of endometriosis is the inspection of the abdominal cavity by laparoscopy and histological examination of biopsies obtained from suspicious lesions. However, non-invasive methods such as imaging modalities, genetic tests, serum or tissue biomarkers are being investigated in the diagnosis due to the risks and cost of surgery that brings to the patient. [80]

Currently, there is no reliable biomarker in the diagnosis of endometriosis. Laparoscopy is still the most reliable method in the diagnosis of endometriosis.

In a review investigating the results of 122 biomarkers of more than 15,000 patients, biomarkers from the family of hormones and cytokines such as activin A, folistatin, urocortin 1, IL-6, IL-33 and TNF-alpha were studies and only data of 4 markers were analyzed after exclusion criteria due to differences in analyzing methods and small sample sizes. The sensitivity for anti-endomysial antibodies was 0.81 and specificity was 0.75, the sensitivity of interleukin-6 was 0.63 and its specificity was 0.69, and the sensitivity for CA-19-9 was 0.36 and the specificity was 0.86. The sensitivity and specificity for CA-125 were found to be 0.40 and 0.9, respectively. However, no marker was found to be reliable in diagnosing endometriosis. [81, 82]

The most studied antigen in the current literature is Ca-125. However, due to it may also increase in ovarian cancer, inflammation, gynecologic and gastrointestinal system diseases, there is no evidence of using Ca125 alone in the diagnosis of endometriosis. [79, 83] In a meta-analysis comprised of more than 1500 patients, the sensitivity and specificity of Ca125 were reported as 52.4% and 92.7%, respectively in the diagnosis of endometriosis. The results >30 IU may be considered sufficient to support the diagnosis in symptomatic patients, whereas its utilization as a screening test is not recommended. [84]

The most commonly studied tissue biomarker is a family member of ubiquitin hydrolase proteins called Protein gene product 9.5 (PGP 9.5). Although it was thought to be a good biomarker, (98-100% sensitivity and 85-100% specificity), recent studies have shown that PGP 9.5 is not sufficient for the diagnosis of endometriosis. [85, 86]

In parallel with advances in the field of genetics in recent years, miRNAs which are non-coding RNA ones with 18-22 nucleotides in length were investigated and it is claimed that they could be

involved in angiogenesis, inflammation, abnormal cell differentiation and invasion causing endometriosis and infertility. [87] It is also found that various miRNA types could increase or decrease in patients with endometriosis.[88] However, there is not enough reliable data to be used in the diagnosis of the disease because they may be affected by cardiovascular diseases, cancer or stress. [89] Also, specifically, thanks to new technologies that enable multiple molecules to be screened at the same time in the diagnosis of complex diseases, recent studies are focused on omics (genomics, transcriptomics, proteomics, metabolomics, etc.) biomarkers. [90] Moreover, in whole genome-wide association studies (GWAS) are investigated the changes in the genome that could be associated with a particular disease, and it was thought that detection of single nucleotide polymorphisms (SNP) could be effective in the diagnosis of chronic complex diseases. [91] In a meta-analysis evaluating GWAS studies of European, American and Japanese patients with stage 3-4 endometriosis, 6 genome region (7p15.2, WNT4, VEZT, CDKN2B-AS1, ID4, and GREB1) SNP changes were detected. However, as the studies on the subject may vary with the societies and disease stage, there is not enough reliable data have been found yet. Besides, in a review of markers obtained from menstrual fluids and endometrial tissues; markers such as CYP19, TIMP-1, and VEGF were found to be significant, but there was insufficient evidence to use them for screening purposes. [92]

In recent years, there are studies on increased levels of HE4 (human epididymis protein, a member of the Whey acidic protein family) 4) in the differential diagnosis of malignant and benign adnexal masses and also in EOC. [93, 94] The sensitivity of HE4 to differentiate ovarian endometriosis from other EOCs in premenopausal patients was found to be 82.1% and specificity was 100%. [93]

Although HE4 levels were independent of the menstrual cycle as opposed to Ca 125, it was claimed that age (> 55 years) [95.96], postmenopausal status, presence of advanced ovarian cancer, impaired renal function and smoking could affect the level of HE4. [97] As an important advantage of HE4, it has been shown to increase 5-8 months before Ca125, especially in detecting recurrences in postoperative EOC follow-up periods. [98]

Recently, in addition to serum markers, various researches are performed especially on tissue markers. [99] In a study, endometriosis-related EOC showed a 40% loss of ARID1A gene expression which is defined as a proto-oncogene. [99, 100] Loss of ARID1A expression was also detected in typical and atypical endometriosis tissues. [101]

Ca 125 which is the most studied biomarker in the diagnosis, it is reliability is still limited. HE4 may be effective in differentiating malignancy especially in premenopausal patients.

In conclusion, the biomarkers studied in the diagnosis of endometriosis and endometriosis-associated EOC were not reliable due to small numbers of case series, different study designs, heterogeneous laboratory methods, and high bias rates.

6. Prognosis in Ovarian Cancers Associated with Endometriosis

According to FIGO ovarian cancer staging system, early stage and low grade means an increase in 5-year survival [102]. Endometriosis related ovarian cancer has been diagnosed at an early age, with a lower stage and grade, therefore it is thought to have a better prognosis [103].

The study of Komiyama et al suggested that when ovarian cancer stage was discarded from being variable, endometriosis related ovarian cancers have a better prognosis. However, in the other studies no significantly difference has been shown between endometriosis related or non-endometriosis related ovarian cancer in terms of 5-year survival [77,103,104].

The chance of early diagnosis of endometriosis-related ovarian cancer may provide better prognosis than ovarian cancers unrelated to endometriosis [42]. Since endometriosis represents tissue with well differentiation, it is not associated with aggressive oriented cancer prognosis. %13 of endometriosis related ovarian cancers are endometrioid carcinoma and the high sensitivity of this histological type to chemotheraphy provides advantage in prognosis [42].

Paik et al. studied the endometriosis related and unrelated ovarian cancers in terms of progression and survival and compared stage, age, lymph node metastasis, Ca125 level and postoperative residue in these groups. Both progression and survival showed significantly better prognosis in endometriosis related ovarian cancers. However, there was no significant difference in terms of survival in multivariate analysis [105].

In conclusion, the association between ovarian cancer and endometriosis is not accepted as a poor prognostic factor.

Endometriosis related ovarian cancers can be diagnosed at an early stage. Association with endometriosis may have better prognosis in ovarian cancer.

7. Endometriosis and Non-Gynecological Cancers

The relationship between endometriosis and non-gynecological cancers has been shown in very few studies in the literature contrary to a large number of strong studies showing the relationship between endometriosis and ovarian carcinoma.[21, 106, 107] The most common of these are breast cancer, thyroid cancer, melanoma/non-melanoma, and non-Hodgkin's lymphoma.

7.1. Endometriosis and Breast Cancer

The relationship between breast cancer and endometriosis is still controversial due to studies reporting positive relationship,[108-110] negative relationship,[69, 111, 112] and no relationship.[21, 74, 113-115] The relationship between endometriosis and breast cancer, which was revealed in a meta-analysis by Gandini et al. in 2018, was investigated in 6000 breast cancer female patients with endometriosis. A total of 32 studies were included in the meta-analysis: 17 were cohort design, 13 were case-control studies and two were cross-sectional studies. In studies included in the meta-analysis, the endometriosis was diagnosed surgically, clinically by an expert during an outpatient examination, through scanning the hospital database and based on patients' statements in patients evaluated for infertility. According to this meta-analysis, there was no relationship between endometriosis and breast cancer. [116] In a retrospective cohort study carried out in Finland, which included a total of 49933 patients with surgically confirmed endometriosis, the risk of breast cancer was reported to be the same as in the normal population and this rate did not differ between endometriosis sub-types. Similarly, rates were found to be similar for ductal and lobular breast cancer. In this study, there was a higher risk of breast cancer particularly in the age groups of 20–29 and 30–39. According to the analysis, increased incidence of breast cancer in young ages was attributed to the fact that young endometriosis patients were extremely symptomatic and they, therefore, received frequent treatment. These treatments may cause additional risk factors for breast cancer. [114]

Data from different studies are not consistent with each other. Brinton et al. reported in their study that the risk of breast cancer was higher in patients with pelvic endometriosis compared to patients with endometriosis. [117]

Similarly, Williams et al. [108] emphasized the increased risk of in-situ breast cancer although they indicated no increase in total breast cancer rates. Mogensen et al. [118] reported an increased risk in patients with endometriosis who were older than 50 years of age. In a study by Chuang et al. investigating the data of 4884 patients with breast cancer, the risk of breast cancer was emphasized to increase significantly in patients with endometriosis and there was a need for further studies with greater population. [110]

However, in contrast to these studies, Farland et al. 119 found no increased risk of breast cancer in premenopausal or postmenopausal patients in their prospective study. Interestingly, Gemmill et al. emphasized low incidence rates for breast cancer in patients with endometriosis.

In that study, the authors suggested that the high breast cancer risk due to hormonal therapy used in patients with endometriosis might be reduced by high rates of oophorectomy. [111]

According to Savalanien et al. [114], patients with endometriosis and young patients with breast cancer may share similar risk factors. Genetic factors included in these risk factors and breast cancer genes 1 and 2 (BRCA1-2) may explain young patients with breast cancer among patients with endometriosis.[120]

No direct relationship has been found between endometriosis and breast cancer in the researchers conducted so far. Both diseases share common risk factors such as infertility, nulliparity and early menarche.

It has been further reported in the current literature that low body mass index and oral contraceptives used in patients with symptomatic endometriosis may be responsible for breast cancer in young patients. [114] Studies have reported that the increase in the rate of in situ cancer in the age range of 40-59 may be due to the more frequent application of imaging techniques for endometriosis patients over the age of 40 compared to the normal population. [108]

Estrogen hormone is held responsible for the development of breast cancer and both diseases occur when this hormone reaches higher levels.

7.2. Endometriosis and Thyroid Cancer

A total of five studies on thyroid cancer was investigated and the data obtained from four of these studies were interpreted as there was a moderate positive relationship between endometriosis and thyroid cancer,[69, 107, 117, 121] however, Melin et al. found no relationship between endometriosis and thyroid cancer in their study carried out in 2010. [69]

The complex relationship of estrogen-progesterone hormones should be considered in the development of breast cancer in the presence of endometriosis. Regular breast examinations are still applicable to all women regardless of the presence of endometriosis.

In a study by Brinton et al. where the types of cancer seen in infertile patients were investigated, the relative risk of thyroid cancer was found to be 4.65 when endometriosis was considered as the primary cause of infertility, however, the relative risk was reported as 2.89 when endometriosis was considered as the secondary cause of infertility. [117]

The increased thyroid cancer risk in patients with endometriosis can be explained by unstable estrogen metabolism and autoimmunity.[121] Estrogen can increase the invasiveness, migration and proliferation of thyroid cancer. It has been further suspected that progesterone may play a key role in the development and growth of thyroid cancer. [121]

However, the relationship between exogenous hormonal therapy and thyroid cancer has not been demonstrated yet. [122] Furthermore, thyroid peroxidase antibodies were found to be higher in patients with endometriosis compared to healthy individuals. [121,122]

Estrogen can increase proliferation, adhesion and invasion of thyroid cells under in vitro conditions.

7.3. Endometriosis, Melanoma and Other Skin Malignancies

Six of 10 studies investigating the relationship between endometriosis and melanoma were reported that there was a positive relationship between them, [21,69, 107, 111, 123], however, three studies reported no relationship [21, 117, 122] and one study reported a negative relationship.[124] In a cohort study carried out in 2014, there was a moderate risk between various colored pigmented skin lesions, nevus density, melanoma family history, and endometriosis, and it was emphasized that there was uncertainty about the underlying mechanism. [125]

A prospective study carried out in France in 2007 showed that there was a significantly increased risk of melanoma in 5959 patients with endometriosis. [126] Similarly, in an 18-year prospective study in 2017, endometriosis has been reported to have an increased correlation with all skin cancers and it has been shown that there was a higher risk of melanoma development rather than squamous cell cancer when the sub-types were taken into consideration. [123]

In a meta-analysis by Gandini et al., the relative risk between melanoma and endometriosis was found to be 1.30 in 10 independent studies examining more than 500 melanoma patients with endometriosis. Significant results were reported in only one of the four studies in basal cell carcinoma which is one of the non-melanoma skin cancer types. [116]

The relationship between endometriosis and melanoma has not yet been clarified due to the diversity of skin lesions and the apparent phenotype characteristics (e.g. white race or ginger hair) of endometriosis patients.

7.4. Endometriosis and Non-Hodgkin's Lymphoma and Other Non-Gynecological Cancer Types

In three of the five studies, a positive correlation was reported between Non-Hodgkin's lymphoma and endometriosis [21, 117, 123, 124], however, one reported a negative relationship 69 and one reported no relationship [111]. Melin et al. reported that endometriosis was a good prognostic factor for non-Hodgkin's lymphoma. [69] It has been suggested that patients with endometriosis are less exposed to human papillomavirus (HPV) due to its relationship with endometriosis and thus, the development risk of pharyngeal and oral carcinomas is reduced by 40%. Pancreatic cancer was observed to decrease in patients with endometriosis. [114-122]

8. Association Between Adenomyosis and Endometrial Cancer

Adenomyosis which is a benign gynecological disease which is characterized by the presence of endometrial gland and stroma in the myometrium and accompanied by hyperplasia and hypertrophy in the surrounding myometrium. Although malignancy occurs in approximately 1% of endometriosis cases, malignant transformation is rarer in adenomyosis. [127]Goumenou et al. demonstrated loss of cellular heterozygosity in adenomyosis for the first time.[128]

There are some clinical symptoms of endometrial adenocarcinoma in the background of adenomyosis including abnormal uterine bleeding, menorrhagia, anemia and weight loss. [129] Malignant transformation of adenomyosis usually occurs in postmenopausal women, however, it is very rare in premenopausal patients. [130] Although it has been suggested that adenomyosis associated with uterine leiomyoma and/or endometrial polyp as a precursor to malignancy, there is not enough evidence. [131,132]

Although adenomyosis has malignant features such as rapid growth, angiogenesis and invasion, progression to malignancy is rare. [129]

Genetic changes, inactivation of specific tumor suppressor genes and mutations may be effective factors. In the study of Goumenou et al., it was stated that loss of heterozygosity may be influential in the initial stages of adenomyosis. [128]

In addition, the DNA mismatch repair genes including hMSH2 and hMLH1, p16INK4 (CDKN2A, cyclin-dependent kinase inhibitor 2A) and GALT (galactose 1 phosphate uridyltransferase) genes have also been implicated in the development of adenomyosis. [128] Loss of heterozygosity in chromosome regions such as 2p22.3-p16.1 and 3p24.2-p22 which codes DNA

mismatch repair genes (hMSH2, hMLH1), may be associated with cancer predisposition in adenomyosis. [128]

Malignant transformation of adenomyosis usually occurs in postmenopausal women. However, the risk factors that cause malignant transformation are not yet clear. [133]

Furthermore, in ectopic endometrial tissue in the adenomyotic focus, bcl-2 expression decreased in contrast to normal endometrial tissue. In addition, progesterone receptor in adenomyosis shows epigenetic variation due to methylation in the promoter region. Progesterone receptor B isoform is hypermethylated in adenomyosis and its expression is decreased simultaneously. [134] Currently, malignant transformation of adenomyosis is thought to be due to endometrial epithelial transmission. It is also thought that malignant transformation may begin with the transformation of the endometrial epithelium into monolayer tumor cells. However, the specific molecular mechanisms of adenomyosis and the risk factors for malignant transformation are still unclear. [127]

Malignant transformation of adenomyosis usually occurs in postmenopausal women. However, the risk factors causing malignant transformation are not clear yet.

In summary, ovarian cancers associated with endometriosis are rare. Various molecular, immune, genetic and environmental factors have been blamed in the etiology. Risk factors include advanced age, mass size, increased estrogenic activity, increased oxidative radicals have been blamed and endometriosis surgery has been reported to minimize these risks. Epidemiological studies have often reported that endometriosis may be associated with clear cell and endometrioid type ovarian carcinoma. Although there is no clear biomarker to date, HE4 and ARID1A seems to be promising. It is thought to have a better prognosis than other EOCs because of early diagnosis. In addition, there is not a close association between endometriosis and non-gynecologic cancers.

9. References

1. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364(9447):1789–1799.

2. Selman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod.2014;29(3):400-412.

3. Vercellini P, Buggio L, Berlanda N, et al. Estrogen-progestins and progestins for the management of endometriosis. FertilSteril. 2016;106(7):1552-1571.

4. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of LaparoscopicallyConfirmed Endometriosis by Demographic, Anthropometric, and Lifestyle Factors. American Journal of Epidemiology.2004;160(8):784–796.

5. Signorello LB, Harlow BL, Cramer DW, Spiegelman D, Hill JA. Epidemiologic determinants of endometriosis: A hospitalbasedcase-control study. Annals of Epidemiology. 1997;7(4):267–274.

6. Dorgan JF, Reichman ME, Judd JT, Brown C, Longcope C, Schatzkin A et al. Relationships of age and reproductivecharacteristics with plasma estrogens and androgens in premenopausal women. Cancer Epidemiology Biomarkers &Prevention. 1995;4(4):381–386.

7. Matalliotakis I, Cakmak H, Fragouli Y, Goumenou A, Mahutte N, Arici A. Epidemiological characteristics in women withand without endometriosis in the Yale series. Archives of Gynecology and Obstetrics. 2008;277(5):389–393.

8. Heilier JF, Donnez J, Nackers F, Rousseau R, Verougstraete V, Rosenkranz K, et al. Environmental and host-associated riskfactors in endometriosis and deep endometriotic nodules: a matched case-control study. Environ Res. 2007;103(1):121–129.

9. Peterson CM, Johnstone EB, Hammoud AO, Stanford JB, Varner MW, Kennedy A, et al. Risk factors associated withendometriosis: importance of study population for characterizing disease in the ENDO Study. Am J Obstet Gynecol.2013;208(6) 451.e451–451.e411.

10. Vercellini P, Eskenazi B, Consonni D, Somigliana E, Parazzini F, Abbiati A, et al. Oral contraceptives and risk ofendometriosis: a systematic review and meta-analysis. Hum Reprod Update. 2011;17(2):159–170.

11. Grodstein F, Goldman MB, Ryan L, Cramer DW. Relation of female infertility to consumption of caffeinated beverages.Am J Epidemiol. 1993;15:1353-1360.

12. Darrow SL, Vena JE, Batt RE, Zielezny MA, Michalek AM, Sharon S. Menstrual Cycle Characteristics and the Risk ofEndometriosis. Epidemiology. 1993;4(2):135–142.

13. Cramer DW, Missmer SA. The epidemiology of endometriosis. Ann N Y Acad Sci. 2002 Mar;955:11–22. discussion 34–6, 396–406.

14. Farland LV, Shah DK, Kvaskoff M, Zondervan K, Missmer SA. Epidemiological and Clinical Risk Factors forEndometriosis. In: D'Hooghe T, editor. Biomarkers for Endometriosis. Springer Science; New York: 2015.

15. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol.1990;162(2):502–514.

16. Bravi F, Parazzini F, Cipriani S, Chiaffarino F, Ricci E, Chiantera V, Viganò P, La Vecchia C. Tobacco smoking and riskof endometriosis: a systematic review and meta-analysis. BMJ Open. 2014; 22;:e006325.

17. Ploteau S, Antignac JP, Volteau C, Marchand P, Vénisseau A, Vacher V, Le Bizec B. Distribution of persistent organicpollutants in serum, omental, and parietal adipose tissue of French women with deep infiltrating endometriosis and circulatingversus stored ratio as new marker of exposure. Environ Int. 2016;97:125-136.

18. Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, et al. A prospective study ofdietary fat consumption and endometriosis risk. Human Reproduction. 2010;25(6):1528–1535.

19.Poole EM, Lin WT, Kvaskoff M, De Vivo I, Terry KL, Missmer SA. Endometriosis and risk of ovarian and endometrialcancers in a large prospective cohort of U.S. nurses. Cancer Causes Control. 2017;28(5):437–445

20. Kumar S, Munkarah A, Arabi H, et al (2011). Prognostic analysis of ovarian cancer associated with endometriosis. Am JObstet Gynecol, 204, 61-67.

21.Melin A, Sparen P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer.Hum Reprod 2006;21:1237–1242.

22. Nezhat F, Datta MS, Hanson V, Pejovic T, Nezhat C, Nezhat C. The relationship of endometriosis and ovarian malignancy:a review. Fertility and Sterility. 2008;90:1559–1570.

23. Hanahan D, Weinberg RA. Thehallmarks of cancer. Cell. 2000;100:57–70.

24. Munksgaard PS, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, geneticand molecular alterations. GynecolOncol. 2012;124:164–169.

25. Fialkow PJ. Clonal origin of human tumors. Biochem Biophys Acta. 1976;458:283–321.

26. Somigliana E, Vigano P, Parazzini F, Stoppelli S, Giambattista E, Vercellini P. Association between endometriosis andcancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol. 2006;101(2):331-341.

27. Otsuka J, Okuda T, Sekizawa A, Amemiya S, Saito H, Okai T, et al. K-ras mutation may promote carcinogenesis ofendometriosis leading to ovarian clear cell carcinoma. Med Electron Microsc. 2004;37(3): 188-192.

28. Sato N, Tsunoda H, Nishida M, Morishita Y, Takimoto Y, Kubo T et al. Loss of heterozygosity on 10q23.3 and mutationof the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: possible sequence progression from benignendometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. Cancer Res. 2000;60(24): 7052-7056.

29. Xiao W, Awadallah A, Xin W. Loss of ARID1A/BAF250a expression in ovarian endometriosis and clear cell carcinoma.Int J Clin Exp Pathol. 2012;5:642–642.

30. Wilbur MA, Shih IM, Segars JH, Fader AN. Cancer Implications for Patients with Endometriosis. Semin Reprod Med,2017;35(1): 110-116.

31. Prowse AH, Manek S, Varma R, Liu J, Godwin AK, Maher ER, et al. Molecular genetic evidence that endometriosis is aprecursor of ovarian cancer. Int J Cancer. 2006;119:556–562.

32. Sato N, Tsunoda H, Nishida M, et al. Loss of heterozygosity on 10q23.3 and mutations of the tumor suppressor gene PTENin benign endometrial of the ovary: possible sequence progression from benign endometrial cyst toendometrioid carcinomaand clear cell carcinoma of the ovary. Cancer Res. 2000;60:7052–7056.

33. Dinulescu DM, Ince TA, Quade BJ, Shafer SA, Crowley D, Jacks T. Role of K-ras and PTEN in the development of Mousemodels of endometriosis and endometrioid ovarian cancer. NatMed. 2005;11:63–70.

34. Sekizawa A, Amemiya S, Otsuka J, Saito H, Farina A, Okai T et al. Malignant transformation of endometriosis: applicationof laser microdissection for analysis of genetic alterations according to pathological changes. Med Electron Microsc.2004;37(2): 97-100.

35. Mandai M, Yamaguchi K, Matsumura N, et al. Ovarian cancer in endometriosis: molecular biology, pathology, and clinicalmanagement. Int J ClinOncol. 2009;14:383–391.

36.Bischoff FZ, Heard M, Simpson JL. Somatic DNA alterations in endometriosis: high frequency of chromosome 17 and p53loss in late-stage endometriosis. J Reprod Immunol. 2002;55:49-64.

37. Akahane T, Sekizawa A, Purwosunu Y, Nagatsuka M, Okai T. The role of p53 mutation in the carcinomas arising fromendometriosis. Int J Gynecol Pathol. 2007;26(3): 345-351.

38. Stamp JP, Gilks CB, Wesseling M, Eshragh S, Ceballos K, Anglesio MS et al. BAF250a Expression in AtypicalEndometriosis and Endometriosis-Associated Ovarian Cancer. Int J Gynecol Cancer. 2016;26(5): 825-832.

39. Samartzis EP, Samartzis N, Noske A, Fedier A, Caduff R, Dedes KJ et al. Loss of ARID1A/BAF250a-expression inendometriosis: a biomarker for risk of carcinogenic transformation? Mod Pathol 2012;25(6): 885-892.

40. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T et al. ARID1A mutations in endometriosis-associated ovariancarcinomas. N Engl J Med. 2010;363(16): 1532-1543.

41. Kurman RJ, Shih IeM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm.Hum Pathol. 2011;42(7): 918-931.

42. Kajiyama H, Suzuki S, Yoshihara M, Tamauchi S, Yoshikawa N, Niimi K. Endometriosis and cancer. Free Radic BiolMed. 2019;133: 186-192.

43. Yamamoto S, Tsuda H, Takano M, Tamai S, Matsubara O. PIK3CA mutations and loss of ARID1A protein expression areearly events in the development of cystic ovarian clear cell adenocarcinoma. Virchows Arch. 2012;460:77–87.

44. Suzuki M, Shigematsu H, Shames DS, et al. DNA methylationassociated inactivation of TGFβ-related genesDRM/Gremlin, RUNX3, and HPP1 in human cancers. Br J Cancer. 2005;93:1029–1029

45. Guo C, Ren F, Wang D, et al. RUNX3 is inactivated by promoter hypermethylation in malignant transformation of ovarianendometriosis. Oncol Rep. 2014;32:2580–2588.

46. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborativeanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breastcancer. Lancet. 1997;350:1047–1059.

47. Beresford SA, Weiss NS, Voigt LF, et al. Risk of endometrial cancer in relation to use of oestrogen combined with cyclicprogestagen therapy in postmenopausal women. Lancet. 1997;349:458–461.

48. Morch LS, Lokkegaard E, Andreasen AH, et al. Hormonetherapy and ovarian cancer. JAMA. 2009;302:298–305.

49. Heaps JM, Nieberg RK, Berek JS. Malignant neoplasms a rising in endometriosis. ObstetGynecol. 1990;75:1023–1028.

50. Oxholm D, Knudsen UB, Kryger-Baggesen N, et al. Postmenopausal endometriosis. Acta Obstet Gynecol Scand.2007;86:1158–1164.

51. Zeitoun KM, Bulun SE. Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target. FertilSteril. 1999;72:961–969

52. Zeitoun K, Takayama K, Sasano H, et al. Deficient 17betahydroxysteroid dehydrogenase type 2 expression inendometriosis: failure to metabolize 17beta-estradiol. J Clin Endocrinol Metab. 1998;83:4474–4480

53. O'Donnell AJ, Macleod KG, Burns DJ, et al. Estrogen receptor alpha mediates gene expression changes and growthresponse in ovarian cancer cells exposed to estrogen. Endocr Relat Cancer. 2005;12:851–866.

54. Matsuzaki S, Murakami T, Uehara S, et al. Expression of estrogen receptor alpha and beta in peritoneal and ovarianendometriosis. Fertil Steril. 2001;75:1198–1205.

55. Feng Huang , Dong Wang , Yongliang Yao , Mei Wang. PDGF signaling in cancer progression. Int J Clin Exp Med2017;10(7):9918-9929

56. Swiersz LM (2002) Role of endometriosis in cancer and tumor development.Ann NY Acad Sci 955: 281–292.

57. Dawson A, Fernandez ML, Anglesio M, Yong PJ, Carey MS. Endometriosis and endometriosis-associated cancers: newinsights into the molecular mechanisms of ovarian cancer development. Ecancermedicalscience. 2018;12:803.

58. Bukulmez O, Hardy DB, and Carr BR, et al (2008) Inflammatory status influences aromatase and steroid receptorexpression in endometriosis Endocrinology 149(3) 1190–1204.

59. Han SJ and O'Malley BW (2014) The dynamics of nuclear receptors and nuclear receptor coregulators in the pathogenesisof endometriosis Hum Reprod Update 20(4) 467–484].

60. Kobayashi H, Imanaka S, and Nakamura H, et al (2014) Understanding the role of epigenomic, genomic and geneticalterations in the development of endometriosis (review) Mol Med Rep 9(5) 1483–1505

61. Toyokuni S (2009) Role of iron in carcinogenesis: cancer as a ferrotoxic disease Cancer Sci 100(1) 9–16

62. Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: a metaanalysis.Br J Cancer. 2014 Apr 2;110(7):1878-1890.

63. Kobayashi H, Sumimoto K, Kitanaka T, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, Kanayama S, ShigetomiH, Haruta S, Tsuji Y, Ueda S, Terao T: Ovarian endometrioma–risks factors of ovarian cancer development. Eur J ObstetGynecol Reprod Biol 2008, 138:187–193.

64. Zanetta G M, Webb M J, Li H. et al. Hyperestrogenism: a relevant risk factor for the development of cancer fromendometriosis. Gynecol Oncol. 2000;79:18–22

65. Worley M J, Welch W R, Berkowitz R S. et al. Endometriosis-associated ovarian cancer: a review of pathogenesis. Int JMol Sci. 2013;14:5367–5379.

66. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovariancancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women withovarian cancer and 87 303 controls. Lancet. 2008;371:303–314.

67.Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT: Oral contraceptive use, reproductive history,and risk of epithelial ovarian cancer in women with and without endometriosis. Am J Obstet Gynecol 2004, 191:733–740.

68. Cottreau CM, Ness RB, Modugno F, Allen GO, Goodman MT. Endometriosis and its treatment with danazol or lupron inrelation to ovarian cancer. Clin Cancer Res. 2003;9:5142–5144.

69. Melin AS, Lundholm C, Malki N, Swahn ML, Sparèn P, Bergqvist A. Hormonal and surgical treatments for endometriosisand risk of epithelial ovarian cancer. Acta Obstet Gynecol Scand 2013;92:546–554.

70. Bulun SE. Endometriosis. N Engl J Med. 2009;360:268–279.

71. Nezhat F, Datta MS, Hanson V, Pejovic T, Nezhat C. The relationship of endometriosis and ovarian malignancy: a review.Fertil Steril. 2008;90:1559–1570.

72. Matsumoto T, Yamazaki M, Takahashi H, et al. Distinct β-catenin and PIK3CA mutation profiles in endometriosisassociatedovarian endometrioid and clear cell carcinomas. Am J Clin Pathol. 2015;144:452–463.

73.Lee WL, Chang WH, Wang KC, et al. The risk of epithelial ovarian cancer of women with endometriosis may be variedgreatly if diagnostic criteria are different:a nationwide population-based cohort study. Medicine (Baltimore) 2015;94:e1633.

74.Kok VC, Tsai HJ, Su CF, Lee CK. The risks for ovarian, endometrial, breast, colorectal, and other cancers in women withnewly diagnosed endometriosis or adenomyosis:a population-based study. Int J Gynecol Cancer 2015;25:968-976.

75. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al., Ovarian Cancer Association Consortium.Lancet Oncol. 2012; 13(4):385-394.

76.Scarfone G, Bergamini A, Noli S, et al. Characteristics of clear cell ovarian cancer arising from endometriosis:A two centercohort study. Gynecol Oncol 2014;133:480–484.

77.Davis M, Rauh-Hain JA, Andrade C, et al. Comparison of clinical outcomes of patients with clear cell and endometrioidovarian cancer associated with endometriosis to papillary serous carcinoma of the ovary. Gynecol Oncol 2014;132:760–766.

78.Xiao W, Awadallah A, Xin W. Loss of ARID1A/BAF250a expression in ovarian endometriosis and clear cell carcinoma.Int J Clin Exp Pathol 2012;5:642–650.

79. Meden H, Fattahi-Meibodi A. CA 125 in benign gynecological conditions. Int J Biol Markers 1998; 13: 231–237.

80. Kiesel L, Sourouni M. Diagnosis of endometriosis in the 21st century. Climacteric 2019; 25:1-7.

81. V Nisenblat, PM Bossuyt, R Shaikh, C Farquhar, V Jordan, CS Scheffers, et al., Blood biomarkers for the non-invasivediagnosis of endometriosis. Cochrane Database Syst Rev. 2016; 7 Cd012179. Art. No.:CD012281.

82. L.M. Maia, A.L. Rocha, H.L. Del Puerto, F. Petraglia, F.M. Reis, Plasma urocortin-1 as a preoperative marker ofendometriosis in symptomatic women, Gynecol Endocrinol 2018; 34: 202–205.

83. Berker B and Seval M Problems with the diagnosis of endometriosis Womens Health (Lond) 2015; 11(5): 597–601.

84. M. Hirsch, J. Duffy, C.J. Davis, M. Nieves Plana, K.S. Khan, Diagnostic accuracy of cancer antigen 125 for endometriosis:a systematic review and meta-analysis, BJOG 2016; 123: 1761-1768.

85. Cetin C, Serdaroglu H, Tuzlali S. The importance of endometrial nerve fibers and macrophage cell count in the diagnosisof endometriosis. Iran J Reprod Med 2013;11:405–414

86. Ellett L, Readman E, Newman M, et al. Are endometrial nerve fibres unique to endometriosis? A prospective case-controlstudy of endometrial biopsy as a diagnostic test for endometriosis in women with pelvic pain. Hum Reprod 2015;30:2808–2815

87. Agrawal S, Tapmeier T, Rahmioglu N, Kirtley S, Zondervan K, Becker C. The miRNA Mirage: How Close Are We toFinding a Non-Invasive Diagnostic Biomarker in Endometriosis? A Systematic Review. Int J Mol Sci 2018;19:pii: E599

88. Maged AM, Deeb WS, Amir AE, et al. Diagnostic accuracy of serum miR-122 and miR-199a in women with endometriosis.Int J Gynecol Obstet 2018;141:14–19.

89. Cosar W, Mamillapalli R, Ersoy GS, et al. Serum microRNAs as diagnostic markers of endometriosis: a comprehensivearray-based analysis. Fertil Steril 2016; 106:402–409

90. N. Mahajan. Endometrial receptivity array: clinical application. J Hum Reprod Sci. 2015; 8: 121–129.

91. N. Rahmioglu DR, Nyholt AP, Morris SA, Missmer GW, Montgomery KT. Genetic variants underlying risk ofendometriosis: insights from meta-analysis of eight genome-wide association and replication datasets. Hum Reprod Update2014; 20: 702–716.

92. Coutinho LM, Ferreira MC, Rocha ALL, Carneiro MM, Reis FM. New biomarkers in endometriosis. Adv Clin Chem.2019; 89:59-77.

93. Huhtinen K, Suvitie P, and Hiissa J, et al Serum HE4 concentration differentiates malignant ovarian tumours from ovarianendometriotic cysts Br J Cancer 2009; 100(8): 1315–1319.

94. Nikolova T, Zivadinovic R, Evtimovska N, Klisarovska V, Stanojevic M, Georgievska J, et al. Diagnostic performance ofhuman epididymis protein 4 compared to a combination of biophysical and biochemical markers to differentiate ovarianendometriosis from epithelial ovarian cancer in premenopausal women. J Obstet Gynaecol Res. 2017;43(12):1870-1879.

95. Babic A, Cramer DW, Kelemen LE, Köbel M, Steed H, Webb PM et al. Predictors of pretreatment CA125 at ovarian cancerdiagnosis: A pooled analysis in the Ovarian Cancer Association Consortium. Cancer Causes Control 2017; 28(5):459–468.

96. Mckinnon B, Mueller MD, Nirgianakis K, Bersinger NA. Comparison of ovarian cancer markers in endometriosis favoursHE4 over CA125. Mol Med Rep 2015; 12(4): 5179–5184.

97. Gislefoss RE, Langseth H, Bolstad N, Nustad K, Mørkrid L. HE4 as an early detection biomarker of epithelial ovariancancer. Int J Gynecol Cancer 2015; 25(9): 1608–1615.

98. Granato T, Porpora MG, Longo F, Angeloni A, Manganaro L, Anastasi E. HE4 in the differential diagnosis of ovarianmasses, Clinica Chimica Acta 2015; 446: 147–55.

99. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, et al. ARID1A mutations in endometriosis associated ovariancarcinomas. New Eng J Med. 2010;363(16):1532-1543.

100. Jones S, Wang TL, Shih IeM, Mao TL, Nakayama K, Roden R, et al. Frequent mutations of chromatin remodeling geneARID1A in ovarian clear cell carcinoma. Science 2010;330 (6001): 228-231.

101. Barreta A, Sarian LO, Ferracini AC, Costa LBE, Mazzola PG, de Angelo Andrade L, et al. Immunohistochemistryexpression of targeted therapies biomarkers in ovarian clear cell and endometrioid carcinomas (type I) and endometriosis. HumPathol. 2018;14: S0046-8177(18)30427-1.

102. Mangili G, Bergamini A, Taccagni G, Gentile C, Panina P, Vigano P et al. Unraveling the two entities of endometrioidovarian cancer: a single center clinical experience. Gynecol Oncol. 2012;126(3): p. 403-407.

103. Erzen M, Rakar S, Klancnik B, Syrjänen K. Endometriosis-associated ovarian carcinoma (EAOC): an entity distinct fromother ovarian carcinomas as suggested by a nested case-control study. Gynecol Oncol. 2001;83(1): 100-108

104. Komiyama S, Aoki D, Tominaga E, Susumu N, Udagawa Y, Nozawa S. Prognosis of Japanese patients with ovarian clearcell carcinoma associated with pelvic endometriosis: clinicopathologic evaluation. Gynecol Oncol. 1999;72(3): 342-346.

105. Paik ES, Kim TJ, Choi CH, Kim BG, Bae DS, Lee JW. Clinical outcomes of patients with clear cell and endometrioidovarian cancer arising from endometriosis. J Gynecol Oncol. 2018;29(2): e18.

106. Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res ClinObstet Gynaecol. 2014;28(5):655-681.

107. Kawaguchi R, Tsuji Y, Haruta S, Kanayama S, Sakata M, Yamada Y, et al. Clinicopathologic features of ovarian cancerin patients with ovarian endometrioma. J Obstet Gynaecol Res 2008;34:872-877.

108. Williams CL, Jones ME, Swerdlow AJ, Botting BJ, Davies MC, Jacobs I, et al. Risks of ovarian, breast, and corpus utericancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2million person years of observation. BMJ 2018;362:k2644.

109. Saraswat L, Ayansina D, Cooper KG, Bhattacharya S, Home AW, Bhattacharya S . Impact of endometriosis on risk offurther gynaecological surgery and cancer: a national cohort study. BJOG 2018;125:64-72.

110. Chuang HC, Wu GJ, Lu YS, Lin CH, Hsiung CA. Associations between Medical Conditions and Breast Cancer Risk inAsians: A Nationwide Population-Based Study in Taiwan. PLoS One. 2015;10:e0143410.

111. Gemmill JA, Stratton P, Cleary SD, Ballweg ML, Sinaii N. Cancers, infections, and endocrine diseases in women withendometriosis. Fertil Steril 2010;94:1627-1631.

112. Morales L, Alvarez-Garriga C, Matta J, Ortiz C, Vergne Y, Vargas W et al. Factors associated with breast cancer in PuertoRican women. J Epidemiol Glob Health 2013;3:205-215.

113. Bertelsen L, Mellemkjaer L, Frederiksen K, Kjaer SK, Brinton LA, Sakoda LC et al. Risk for breast cancer among womenwith endometriosis. Int J Cancer 2007;120:1372-1375.

114. Saavalainen L, Lassus H, But A, Tiitinen A, Harkki P, Gissler M et al. A cohort study of 49 933 women with surgicallyverified endometriosis increased incidence of breast cancer below the age of 40. Acta Obstet Gynecol Scand 2019;8.

115. Baron JA, Weiderpass E, Newcomb PA, Stampfer M, Titus-Ernstoff L, Egan KM et al. Metabolic disorders andbreast cancer risk (United States). Cancer Causes Control 2001;12:875-880.

116. Gandini S, Lazzoroni M, Peccetori FA, Bendinelli B, Saieva C, Palli D et al. The risk of extra-ovarian malignancies amongwomen with endometriosis: A systematic literature review and meta-analysis. Crit Rev Oncol Hematol 2019;134:72-81.

117. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis.Am J Obstet Gynecol 1997;176:572-579.

118. Mogensen JB, Susanne KK, Mellemkjær L Jensen A et al. Endometriosis and risks for ovarian, endometrial andbreast cancers: A nationwide cohort study. Gynecol Oncol 2016;143:87-92.

119. Farland LV, Tamimi RM, Eliassen AH, Spiegelman D, Hankinson SE, Chen WY et al. Laparoscopically ConfirmedEndometriosis and Breast Cancer in the Nurses' Health Study II. Obstet Gynecol 2016;128:1025-1031.

120. Anifantaki F, Boutas I, Kalampokas T. Association of endometriosis and breast cancer: mini review of the literature. ArchGynecol Obstet 2016;293:5-10.

121. Braganza MZ, Berrington AG, Schonfeld SJ, Wentzensen N, Brenner AV, Kitahara CM. Benign breast and gynecologicconditions, reproductive and hormonal factors, and risk of thyroid cancer. Cancer Prev Res (Phila) 2014;7:418-425.

122. Saavalainen L, Lassus H, But A, Tiitinen A, Härkki P, Gissler M et al. A Nationwide Cohort Study on the risk of nongynecologicalcancers in women with surgically verified endometriosis. Int J Cancer 2018;143:2725-2731.

123. Farland LV, Lorrain S, Missmer SA, Dartois L, Cervenka I, Savoye I et al. Endometriosis and the risk of skin cancer: aprospective cohort study. Cancer Causes Control 2017;28:1011–1019.

124. Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA. Postmenopausal cancer risk after selfreportedendometriosis diagnosis in the Iowa Women's Health Study. Cancer 2002;94:1612-1618.

125. Kvaskoff M, Jiali Han J,Qureshi AA, Missmer SA. Pigmentary traits, family history of melanoma and the risk ofendometriosis: a cohort study of US women. Int J Epidemiol 2014;43:255-63.

126. Kvaskoff M, Mesrine S, Fournier A, Boutron-Ruault MC, Clavel-Chapelon F. Personal History of Endometriosis andRisk of Cutaneous Melanoma in a Large Prospective Cohort of French Women. Arch Intern Med 2007;167:2061-2065.

127. Yuan H, Zhang S. Malignant Transformation of adenomyosis:literature review and meta-analysis, Arch Gynecol Obstet.2019;299:47-53.

128.Goumenou AG, Arvanitis DA, Matalliotakis IM, Koumantakis EE, Spandidos DA. Loss of heterozygosity in adenomyosison hMSH2, hMLH1, p16Ink4 and GALT loci. Int J Mol Med. 2000;6:667-671.

129. Koike N, Tsunemi T, Uekuri C, Akasaka J, Ito F, Shigemitsu A, Kobayashi H. Pathogenesis and malignant transformationof adenomyosis (review). Oncol Rep. 2013 ;29:861-7.

130.Kazandi M, Zeybek B, Terek MC, Zekioglu O, Ozdemir N, Oztekin K. Grade 2 endometrioid adenocarcinoma arisingfrom adenomyosis of theuterus: report of a case. Eur J Gynaecol Oncol 2010;31:719–721.

131.Ismiil ND, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Thomas G, Ackerman I, Covens A, Khalifa MA.Adenomyosis is associated with myometrial invasion by FIGO 1 endometrial adenocarcinoma. Int J Gynecol Pathol 2007;26:278–283.

132.Mori M, Furusawa A, Kino N, Uno M, Ozaki Y, Yasugi T. Rare case of endometrioid adenocarcinoma arising from cysticadenomyosis. J Obstet Gynaecol Res 2015;41:324–328.

133. Jones RK, Searle RF, Bulmer JN. Apoptosis and bcl-2 expression in normal human endometrium, endometriosis andadenomyosis. Hum Reprod. 1998 Dec;13(12):3496-502.

134.Jichan N, Xishi L, Guo SW. Promoter hypermetilation of progesterone receptor B (PR-B) in adenomyosis and itsrectification by a histone deacetylase inhibitör and a demethylation agent. Reprod Sci. 2010 Nov;17(11):995-1005