Ovarian endometriosis as a premalignant condition: epidemiological, histological and molecular evidence

Abstract
Endometriosis is a common monoclonal benign proliferative disorder that may give rise to pelvic malignancy. Epithelial ovarian carcinoma is responsible for a large proportion of gynaecological cancer-associated deaths. Early diagnosis is difficult and screening is generally unsuccessful. Knowledge of the risk factors for the development of endometriosis and progression to malignancy may assist in identifying women at risk of developing endometriosis-related neoplasm.

The associations between infertility, endometriosis and the development of cancer are reviewed in this article. Proliferative growth, metaplasia, hyperplasia and atypia are identified as proliferative disorders in endometriosis and atypia is considered a premalignant lesion. Several endometriosis-related pelvic malignancies have been described, and these all develop from the multipotent Müllerian cell differentiating into epithelial and/or stromal components. The probable histological type depends on the site of the endometriotic lesion and the population group.

Cytogenetic and specific gene alterations that are involved in the carcinogenetic process are described briefly and these may help to predict risk of malignancy or to confirm histological subtype.

The importance of endometriosis as a precursor of ovarian and related malignancies was probably seriously underestimated in the past. Advances in molecular testing, histology and our understanding of oncogenesis may empower us to help prevent these devastating diseases.

Introduction
Endometriosis affects between seven and 10% of the reproductive age female population and around 20% of women presenting with infertility. Different described types include peritoneal disease (superficial invasion), uterosacral or posterior cervical disease (deeply invasive) and ovarian lesions (endometriomas). Myometrial invasion by endometrial glands, called adenomyosis, was previously recognised as a separate disease, but it frequently co-exists and shares etiological factors with extrauterine endometriosis.1 Interestingly, most patients have a single form of the disease rather than a field effect.

Ovarian epithelial carcinoma is less common than endometriosis, affecting 1-4% of women. It has an aggressive clinical course and is an important cause of gynaecological cancer mortality. Between 16 and 30% of these tumours will have endometrioid histological features, resembling carcinoma of the uterine corpus.2

These tumours are thought to arise from the surface epithelium of the ovary (or adjacent multipotential secondary Müllerian mesothelium) or from the epithelium of existing endometriosis.3

In this article the development of neoplastic disease from ovarian endometriosis will be explored. Important aspects that will be addressed are data about the aetiology and risk factors of endometriosis and related neoplastic ovarian lesions, described associations between endometriosis and malignancy, the histology of these diseases, endometriosis-related nonmalignant and malignant conditions, and finally the cellular and inherited genetics.

Aetiology and risk factors for endometriosis and related neoplastic ovarian lesions

The most widely accepted aetiological theory is that pelvic endometriosis arises from implantation of
menstrual blood disseminated into peritoneal and pelvic structures. The incidence of endometriosis is undoubtedly higher in patients with high volume regurgitation but other factors associated with a higher risk of implantation and uncontrolled growth of these cells are not well described.³

It is generally believed that multiple genetic, environmental and immunological aspects, as well as angiogenic and endocrine factors influence the development and progression of endometriosis. Similar factors probably lead to the malignant transformation of a subset of endometriotic lesions. Genetic, hormonal and immunological factors play important roles, but specific genetic alterations on cellular or germline genetic level have not been identified. Many of these aetiological factors are shared between benign proliferative disorders, benign tumours and some malignancies of the female genital tract.²

Almost all authors who studied the immune system and endometriosis, found immunity to be altered in women with endometriosis. The immune changes are mostly local but involve both humoral and cellular immunity. These immune system alterations favour the invasive behaviour of ovarian neoplasms and will favour malignant transformation of ovarian endometriosis.⁴ Ovarian cancer progression and dissemination is also significantly enhanced by immune suppression. In addition, important associations have recently been found between various autoimmune diseases (Sjogren's syndrome, systemic lupus erythematosus and thyroiditis) and endometriosis by showing an increased incidence (even 20 times) of these diseases in endometriosis sufferers.²

Chronic inflammation may play an important role in the genesis of endometriosis or ovarian cancer, and previous works implicated talc and asbestos exposure, pelvic inflammatory disease and the protective effect of tubal ligation and hysterectomy.³ These factors are believed to impact via the inflammatory reaction, cytokines, prostaglandins, inflammatory cell change and oxidative stress.

An association exists between steroid hormone levels, endometriosis and ovarian cancer. Most evidence is epidemiological and suggests a relative excess of oestrogen as a factor in the formation of endometriosis and ovarian cancer. Progestogen could be a protective hormone, probably via stimulation of apoptosis and the oestrogen-opposing effect. This notion is supported by the preventative effect of the oral contraceptive pill, pregnancies and prolonged breastfeeding in epidemiological studies.

Unopposed oestrogen is a risk factor for both endometriosis and ovarian cancer.⁷ Numerous studies suggest that oestrogen and also tamoxifen play important roles in the pathogenesis of all the related tumours.⁶ This suggests at least a theoretical risk for an iatrogenic increase in incidence. Tamoxifen is linked to endometriosis progression, endometrial proliferative disorders within endometriosis and endometrioid adenocarcinoma in endometriosis. Borderline endometrioid neoplasia and ovarian adenofibroma have been described in association with tamoxifen use.⁶

Angiogenesis and growth factors may play a role in the development of both endometriosis and related ovarian cancers. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor were investigated and related to microvessel count.⁸ An association between an increase in VEGF in endometriosis-associated ovarian cancer was demonstrated when compared with benign endometriosis.¹⁰

Association between endometriosis and malignancy

Gynaecological cancer

An excess incidence of ovarian cancer in infertile women, women stimulated with ovulation induction hormones and women with endometriosis has long been suspected, described, discussed and disputed. It is not possible to identify a single or the most important aetiological factor in these women, as many potential reasons for an elevated ovarian cancer risk coexist.¹¹,¹²

Many authors have shown convincing evidence in a large percentage of nonuterine endometrioid carcinomas that these neoplasms may develop from ovarian endometriosis. Atypical endometriosis can be demonstrated in the majority of cases with endometrioid carcinoma.⁴ It is now certain that a strong association exist between particularly long-standing ovarian endometriosis and endometrioid, as well as clear cell adenocarcinoma of the ovary. Recent pathology-based studies examined the incidence of malignancy in endometriosis or examined the incidence of endometriosis in ovarian cancer. Alternatively authors simply searched their databases for patients with a combination of the two diagnoses and then examined or reviewed all these patients.

In a series of 1000 consecutive cases of surgically proven endometriosis the incidence of coexisting cancer was found to be as high as 5.5%. This carefully executed pathological study does not include the risk of future cancer.¹³ Five per cent of patients with ovarian endometriosis on histology had coexisting ovarian cancer, while only 1% of patients with extraovarian endometriosis had coexisting ovarian cancer. This group also report an intimate association between extraovarian endometriotic foci and the
development of extraovarian clear cell or endometrioid adenocarcinoma and adenosarcomas. An increased incidence of coexistent endometrial pathology and cancer is reported in patients with endometriosis-associated extraperitoneal cancer.14

In a Japanese study of 127 consecutive ovarian cancers, evidence of endometriosis (typical and atypical) could be demonstrated in a surprisingly high number of 37 patients.15,16 The series is atypical compared to those done in Western countries as it consisted of 43 patients with clear cell carcinoma, seven with endometrioid, 60 with serous papillary and 17 with mucinous carcinoma. The clear cell type is much more common in Japan, and was most strongly associated with endometriosis. They could demonstrate histological transition from typical to atypical endometriosis and then to carcinoma in a surprisingly large proportion of specimens (22 and 23 cases respectively).

Although the increased susceptibility in women with endometriosis to develop ovarian clear cell and endometrioid carcinoma is proven and widely accepted, the magnitude of this risk is unknown.1 and endometrioid carcinoma is proven and widely accepted, the magnitude of this risk is unknown.1 The series is atypical compared to those done in Western countries as it consisted of 43 patients with clear cell carcinoma, seven with endometrioid, 60 with serous papillary and 17 with mucinous carcinoma. The clear cell type is much more common in Japan, and was most strongly associated with endometriosis. They could demonstrate histological transition from typical to atypical endometriosis and then to carcinoma in a surprisingly large proportion of specimens (22 and 23 cases respectively).

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This group reports a relative risk of 4.2 for ovarian cancer in women followed up for more than ten years after diagnosis of ovarian endometriosis. This finding was in spite of a high incidence of salpingo-oophorectomy.

It is clear that ovarian endometriosis carries a much higher risk than extra-ovarian endometriosis for the development of cancer in general and specifically for the development of an ovarian neoplasm. The development of extraovarian neoplasms is less well studied and the incidence of malignancy in this subgroup unknown.

**Nongynaecological cancer**

Endometriosis has been linked unconvincingly to an increased incidence of various nongynaecological malignancies. These include malignant melanoma, breast and haematological cancers (non-Hodgkin's lymphoma). Large differences exist between publications18 with more cancers and higher risks reported after histological or hospital diagnosis than after self-reported endometriosis. These differences may reflect the inaccuracy of self-reported diagnoses, a stronger association with more severe disease, population differences or inherent methodological problems.

**Histology of endometriosis-related nonmalignant and premalignant conditions**

Pelvic endometriosis is described and defined as an ectopic lesion consisting of both endometrial glandular cells and endometrial stromal cells. These lesions are monoclonal in origin.19 Endometriotic proliferation occurs mainly under the influence of steroid hormones and is common in premenopausal women. Proliferative endometriosis was described in postmenopausal women and occurs typically in those receiving tamoxifen or unopposed oestrogen therapy, especially high dosage or oestrogen implants.

The definition, description and frequency of atypical endometriosis is less certain. These lesions are more frequent in endometriomas of the ovary and are considered to be premalignant. Malignant transformation occurs more frequently in the ovary than in extraovarian endometriosis.20

When epithelial abnormalities were studied in cystic ovarian endometriosis, high incidence of metaplasia (12%), hyperplasia (9,4%), atypia (6%) and carcinoma (4%) were found in 388 patients. More changes occurred in older women.21 In a similar study of Japanese women, the incidence of atypia was found to be higher at 12%.22

**Histology of endometriosis-related malignant conditions**

Sampson (1925) first developed the criteria for the diagnosis of malignancy developing in endometriosis and this was later modified by Scott.23 These criteria for endometriosis-related malignancy are still widely accepted.

Extraovarian endometriosis-related malignancies are more likely to be endometrioid, adenosquamous, papillary or not otherwise specified adenocarcinoma, adenosarcoma or endometrial stromal sarcoma. Endometriosis-associated carcinomas that occur at a younger age are mostly endometrioid or clear cell type, usually diagnosed in early stage and have a relatively good prognosis.24 Many recent reviews and studies confirm these findings.25,27 It is probable that the aetiology of cancer occurring in older women is often overlooked, the clinical picture is not so well described and therefore the importance of endometriosis-related cancer is underestimated.

Ovarian endometrioid carcinoma is defined as a primary epithelial ovarian tumour with a histological appearance similar to endometrioid carcinoma of the endometrium. Stanton first described it in 1961 and recorded an incidence of about 24% at the International Federation of Gynecology and Obstetrics (FIGO) cancer committee in Stockholm.28

In the ovary the most common types of endometriosis-related malignancy are clear cell and endometrioid adenocarcinoma. Ovarian clear cell carcinoma is
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Inherited genetic factors play an important role, although no clear Mendelian pattern of inheritance should be expected in multifactorial diseases. Inherited factors are likely to influence susceptibility, partly explaining the increased incidence in family members. Allelic differences in drug-metabolising enzymes are inherited and have recently been implicated in the development of endometriosis.

Changes in endometriosis including morphological atypia, hyperplasia and other epithelial changes result from cellular genetic changes and thus carcinogenesis is an accumulation of genetic mistakes of which the order seems unimportant.

**Cytogenetic changes in ovarian tumours**

Simple numeric chromosomal changes occur in a variety of ovarian tumours. Most reports of cytogenetic changes are found in the older literature. In benign and borderline epithelial tumours nonspecific numeric changes occur, with aneuploidy implicated in more aggressive tumour biology, while granulosa cell tumours most often contain monosomy 22, trisomy 12 and 14. Tumours of low malignant potential and early lesions often contain gains at 3q, 8q, 20q. These changes are used to detect the probable region for more common specific gene alterations.

**Specific genetic alterations in endometriosis and ovarian carcinoma**

**K-ras**. Activation of the K-ras proto-oncogene is mostly by point mutation, occurs in about 30% of endometrial cancer (mostly in the K-ras). It was also demonstrated in precursor lesions, suggesting involvement at the early stages of carcinogenesis. Various scientists have investigated the role of the K-ras gene and protein in endometriosis, ovarian endometroid adenocarcinoma and malignant transformation. K-ras mutations were found in clear cell carcinoma but not in the benign or atypical lesions, suggesting K-ras to be an important initiator of malignancy. Peritoneal endometriosis can be induced in mice by adding oncogenic K-ras using an adenoviral vector.

**Beta-catenin**. Beta-catenin plays an important role in early and well-differentiated endometrial cancer, this gene mutation being associated with early carcinogenesis, favourable pathology and good outcome. The gene has not been studied extensively in ovarian cancer. In one study of eight borderline endometrioid ovarian tumours, β-catenin mutations...
were demonstrated in seven of the cases, all with normal immunostaining.39

HER 2/neu or c-erbB-2. The importance of this oncogene in ovarian cancer is currently unclear, but available evidence does not suggest direct involvement in carcinogenesis but rather a prognostic value.40,41 In endometriosis no expression was found in one study.42

P53. Involvement of the P53 gene is usually shown by immunohistochemical demonstration of over-expression of the p53 protein or by mutation analysis of the gene itself. Alterations in the P53 gene (by mutation analysis) have been found in 42% of serous and 42-65% of endometrioid ovarian adenocarcinomas.43,44 Staining is infrequent in benign tumours.44,45 The P53 gene probably plays an important role in malignant transformation of ovarian endometriosis. Endometrial carcinomas positive on p53 immunostaining are associated with adenomyotic lesions that are also positive for the oncogene, suggesting either a field effect or an adenomyotic precursor to the endometrial cancer.46

BRCA 1 and BRCA 2. Involvement of the BRCA genes in sporadic breast and ovarian cancer started receiving research attention in the last decade. While initial studies found BRCA gene mutations in very few sporadic cancers, it is becoming clear that these tumour suppressors do play an important role in tumorigenesis and have a very intricate interaction with other known oncogenes and tumour suppressor genes. Gene inactivation may occur by mutation or by promoter methylation, i.e. epigenetic function loss. BRCA1 inactivation may occur in up to 40% of high grade ovarian cancers and seem to be associated with P53 or PTEN inactivation.47

BCL-2. The proto-oncogene BCL-2 inhibits programmed cell death by counteracting the action of p53, which induces apoptosis. Several groups have included bcl-2 staining in their immunohistochemical studies on malignant transformation of ovarian endometriosis, but produced results that are either non-significant or difficult to interpret.40,44,45

DNA repair genes, microsatellite instability (MSI) and loss of heterozygosity (LOH). MSI has been shown to correlate strongly with methylation of the hMLH1 promoter region causing inactivation of the hMLH1 gene, causing defects in the DNA repair system.49 Higher rates of MSI are found in endometriosis-associated cancers and in endometroid adenocarcinomas than in nonendometroid ovarian cancer.50 Hypermethylation of both hMLH1 and PTEN with inactivation of protein expression were also demonstrated in atypical endometriosis.51 LOH at the PTEN locus is a particularly frequent finding in clear cell carcinomas (around 30%)52,53 and in endometrioid adenocarcinomas (approximately 60%).54

PTEN. The incidence of somatic mutations in the PTEN gene in endometroid endometrial cancer is the highest of any primary malignancy analysed so far with frequencies reported from 40% to 76%. It is suspected that the gene also plays a role in ovarian endometrioid cancer. Various researchers have looked at PTEN involvement in both ovarian cancer and endometriosis by determining loss of heterozygosity on 10q23.3 and by immunohistochemistry. Studies using direct mutation analysis are scarce.

Conclusion

The importance of endometriosis as a precursor to ovarian cancer is still largely unknown and probably differs among populations. The disease is a much more important precursor of endometrioid and clear cell carcinoma than of the other histological types. It is likely to be underestimated in historical studies and its perceived importance will probably increase in the future.

Ovarian neoplasms display a wide range of histological phenotypic patterns. The histological pattern and genotype are related and can be predicted by the genetic aberrations and vice versa. Currently we know that genetic alterations are tumour specific and that the incidences of particular mutations differ from cancer to cancer. We look forward to predicting or subtyping cancers on the grounds of genotype in the near future.

The difficulties presented by the identification and description of a premalignant precursor led to the notion that ovarian epithelial cancer predominantly arises de novo and not through benign or borderline precursors. The accumulation of genetic anomalies in ovarian cancer while appears likely, these probably do not correlate with identifiable histological entities like polyps or adenomas. Therefore molecular genetic studies offer the best hope to understand the carcinogenetic process. These studies may also provide us with a better understanding of the relation between genetic alterations and tumour types.

While simple chromosomal numeric changes were demonstrated in benign and borderline epithelial tumours and in stromal tumours, invasive epithelial ovarian cancers show complex chromosomal changes involving genes that regulate cell proliferation, apoptosis and that play a role in the tyrosine kinase signalling cascade.55 More aggressive neoplasms typically have more gene aberrations.

Knowledge of the risk factors, associations with malignancies and the histological as well as genetic
profile should enable the clinician to recognise endometriosis-related malignancy. It is hoped that the identification of risk will help prevent ovarian malignancy in high-risk women. Prophylactic surgical removal is an effective way to prevent ovarian cancer, while women at a moderately increased risk require at least careful screening.

References
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