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Endometriosis as a model for inflammation–hormone interactions in ovarian and breast cancers

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ABSTRACT

Chronic inflammation has been implicated in a variety of cancers. In this review, we consider associations between endometriosis and cancers both local (ovarian) and distant (breast). We review the epidemiological data linking endometriosis to ovarian and breast cancers. We then consider evidence for a role for sex steroid hormones and for inflammation in the aetiology of each of these cancers. Finally, we consider that endometriosis may promote alterations in sex steroid hormones and inflammatory mediators. A possible explanation for the association between endometriosis and these reproductive cancers may then be local and systemic enhancement of aberrant inflammatory and hormonal mediators. If this hypothesis is true, endometriosis may need to be considered as a risk factor for ovarian and breast cancers, triggering increasingly intensive surveillance. Moreover, treatments for endometriosis may require consideration of the impact on long-term cancer risk.

1. Introduction

Chronic inflammation induced by infections and irritants has been implicated in one-sixth of incident cancers worldwide.[1–3] Just a few examples of non-infectious, chronic inflammants and linked cancers include asbestos fibres and mesothelioma;[4] inflammatory bowel disease and colon cancer; and mastitis and breast cancer.[5] Previously, we proposed that inflammatory exposures may also promote the development of ovarian cancer.[6,7] These examples all involve inflammation and tumour development within the same tissue. Systemic inflammatory diseases and their treatments (e.g., rheumatoid arthritis and TNF-α therapy) have generally been linked to lymphoproliferative, rather than organ-specific malignancies.[8]

In this review, we consider associations between endometriosis, defined by the presence of endometrial foci outside the endometrium, and cancers both local (ovarian) and distant (breast). We suggest that endometriosis may promote both tissue-specific and systemic alterations in sex steroid hormones and inflammatory mediators. Thereby, endometriosis may represent a model, wherein inflammatory–hormonal interactions promote both local and distant carcinogenesis.

2. Epidemiological data linking endometriosis, ovarian cancer and breast cancer

Epidemiological studies have consistently supported a link between endometriosis and cancer. Brinton and colleagues

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assessed cancer outcomes among 20,686 women in Sweden who had been hospitalised with endometriosis.[9] Cancer outcomes were identified through the National Swedish Cancer Registry after a mean of 11.4 years of follow-up. Significant excess risks were observed for ovarian cancer (standardised incidence ratio 1.9, 95% confidence interval (CI) 1.3–2.8), breast cancer (1.3, 1.1–1.4) and non-Hodgkin's lymphoma (1.8, 1.2–2.6). The risk of ovarian cancer was elevated 4.2-fold among women with a long-standing history of ovarian endometriosis. In a more recent retrospective cohort study conducted in the United States of America (USA), Brinton and colleagues confirmed the relationship between endometriosis and ovarian cancer (standardised incidence ratio 2.5, CI 1.3–4.2), and showed a particularly strong relationship between endometriosis resulting in infertility and ovarian cancer (standardised incidence ratio 4.2, CI 2.0–7.7).[10]

Supporting these findings, the 4000 members of the Endometriosis Association completing a health survey[11] reported cancer occurrences that were 5-fold higher for ovarian cancer, 6-fold higher for breast cancer, and 2.5-fold higher for non-Hodgkin's lymphoma than expected rates among women in the general population.

Several case-control studies have confirmed the association between endometriosis and ovarian cancer. Ness and colleagues, in a case-control study of 767 women with epithelial ovarian cancer and 1367 controls,[6] after adjustment for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy and breastfeeding, demonstrated that women with ovarian cancer were 1.7-fold more likely (95% CI 1.2–2.4) to report a history of endometriosis. In a further pooled study of 13,000 women examining the relationships among infertility and ovarian cancer, ovarian cancer was more likely among subfertile women, and particularly among women whose infertility had been diagnosed as resulting from endometriosis (odds ratio (OR) 1.9, 95% CI 1.2–2.9).[12] The only other type of infertility significantly linked to ovarian cancer was infertility of unknown cause (OR 1.5, 95% CI 1.3–1.7), a disorder that hormonal studies suggest may be closely related to endometriosis.[13] The associations between ovarian cancer and either infertility due to endometriosis or infertility due to unknown cause persisted after adjustment for multiple confounding factors. Oral contraceptives, parity and tubal ligation or hysterectomy protected women with endometriosis from developing ovarian cancer.[14]

A record-linkage study involving more than 15,000 women in Sweden addressed the link between endometriosis and breast cancer. Although pre-menopausal oophorectomy was associated with a 50% reduction in breast cancer risk, there was a non-significant increase in breast cancer risk among women whose indication for oophorectomy was endometriosis. Moreover, hysterectomy without oophorectomy was associated with an increase in breast cancer risk when the indication was severe endometriosis.[15] Not all epidemiological studies have been positive. Three small retrospective studies designed to assess infertility found no relationship between infertility from endometriosis and ovarian cancer.[16–18] Two of these, however, found relationships between infertility of unknown cause and ovarian cancer.[17,18] Finally, among women from the Iowa Women's Health Study, self-reported endometriosis was not associated with ovarian or breast cancer, but was significantly associated with risk for non-Hodgkin's lymphoma.[19] Nonetheless, most epidemiological studies support a link between endometriosis and cancer, specifically to ovarian and breast cancers.

3. Clinical data linking endometriosis and ovarian cancer

Although, to our knowledge, the only clinical data that demonstrate an association between endometriosis and breast cancer are studies showing that women using tamoxifen for breast cancer may develop endometriosis (presumably on the basis of a pro-oestrogenic effect (see below))[20,21] there are compelling clinical data relating endometriosis and ovarian cancer. Pathological case series have provided evidence for the transformation of endometriosis into malignancy.[22–32] Heaps and colleagues noted that 165 published cases showed malignant transformation of endometrial implants,[22] almost 80% occurring within ovarian endometriosis. The overall frequency of malignant transformation was estimated to be 0.3–0.8%.[22,31] More recent, larger pathology series (up to 1000 cases) have found ovarian cancer in 5–10% of ovarian endometriotic lesions.[29,33] Endometrioid (up to 60% of lesions) and clear-cell (up to 15%) tumours predominate in proportions higher than have been found among ovarian cancers in general (10–20% and 3–10%, respectively),[34] demonstrating the distinctive, albeit not exclusive, relationship between endometrioid and clear-cell ovarian cancers and endometriosis. One particularly compelling case report documented a biopsy showing atypia within ovarian endometriosis, followed 3 years later by clear-cell ovarian carcinoma in a re-biopsy from the same ovary.[26]

With regard to endometriosis occurring within ovarian cancers, Sainz de la Cuesta and colleagues found endometriosis among about 40% of women with stage I endometrioid or clear-cell ovarian carcinoma, about one-third of which represented carcinomas arising out of endometriosis.[23] Similar results have been reported by others. Endometriosis has generally been found in 21–54% of clear-cell and endometrioid tumours and in 3–9% of serous, mucinous and other tumours.[24,27,35,36] Overall, then, pathology and clinical data strongly support the idea that malignant transformation may occur in perhaps 5–10% of women found at surgery to have ovarian endometriosis. In comparison, the general population lifetime risk of ovarian cancer is only 1.5%.

4. Inflammation and cancer

How might endometriosis elevate the risk of both local and distant cancers? We propose a mechanism influenced by inflammation and steroid hormones. Chronic inflammation results in oxidative stress,[37] necrosis and compensatory cell division. Rapid cell division gives rise to an even greater need for DNA repair with its attendant potential for replication errors, which, particularly when they occur at key regulatory sites, such as p53, increase the risk of mutagenesis.[1] Finally, inflammation involves the release of cytokines and growth factors. Although how the specific biology of chronic inflammation relates to cancer is unknown, increasing agreement

focuses on the balance between the two broad arms of the immune response: cell mediated immunity (CMI) and humoural immunity (HI).[2] CMI is associated with CD4+ lymphocytes that produce non-specific pro-inflammatory cytokines (also called T-helper 1 (Th-1) cytokines). HI is associated with CD4+ lymphocytes that produce immune suppressive cytokines (also called T-helper 2 (Th-2) cytokines). Th-1 cytokines include interferon-γ, TNF-α, and IL-1α and IL-lβ. Th-2 cytokines include IL-4, IL-10 and TNF-β. Some cytokines, such as IL-6, have been classified with Th-1 cytokines by some authors and with Th-2 by others.[3,38] Pro-inflammatory cytokines are expressed in the presence of infections and inflammants. They upregulate cyclo-oxygenase (COX)-2, the enzyme that catalyses the synthesis of prostaglandins. Prostaglandins, in turn, decrease cell differentiation, inhibit apoptosis[39] increase tumour cell proliferation[40] and induce angiogenesis through growth factors and matrix metalloproteases.[41] In particular, cytokines such as IL-6 and VEGF are pro-angiogenic, supporting the growth of new blood vessels required for breast tumour growth.[42,43] All of these processes increase the risk for promulgating DNA mutations and tumour spread. Th-2 cytokines, on the other hand, inhibit Th-1 cytokines and COX-2 expression.[2,44] Certain chronic inflammatory conditions associated with tumour development have been associated with an abundance of Th-2 and a paucity of Th-1 cytokines; however, an imbalance of either Th-1 or Th-2 cytokines, prostaglandins, and COX-2 may play a role in carcinogenesis.

4.1. *Inflammation and breast cancer*

Indirect epidemiological evidence of a link between inflammation and breast cancer comes from studies showing protection by non-steroidal anti-inflammatory drugs (NSAIDs) and risk from antibiotics. NSAIDs inhibit breast tumour cell growth in vitro and in animal models.[45–49] Both case-control and cohort studies suggest that NSAIDs reduce breast cancer risk.[50–68] In the Women's Health Initiative Observational Study, a cohort of more than 80,000 women, regular NSAID use for 5+ years was associated with a 19% decrease in the relative risk (RR) of breast cancer (RR 0.81, 95% CI 0.68–0.97).[51] Results from the Long Island Breast Cancer Prevention Project suggest that this protection may be limited to post-menopausal women (ibuprofen OR 1.08 versus 0.74 for pre-menopausal versus post-menopausal women; aspirin OR 0.89 versus 0.73, pre-menopausal versus post-menopausal women).[52] In contrast, the use of prescribed antibiotics may elevate the risk for breast cancer. In a case control study of more than 10,000 women, Velicer and colleagues demonstrated that antibiotic use was more common in breast cancer cases and particularly in cases who had used antibiotics for longer duration.[69] Although there are many potential explanations for this unique finding, one is that the link might be accounted for by antibiotic treatment of chronic inflammatory conditions.[70]

More direct evidence that inflammation plays a role in breast carcinogenesis follows. Within the normal human breast, the Th-1 cytokine IL-1 controls the expression of growth factors[71] and in breast tumours, IL-1 production results in an autocrine and paracrine induction of pro-metastatic genes[72] including proteolytic enzymes involved in tumour growth and metastasis, such as matrix metalloproteinase (MMP)-1,2,3 and 9.[73] Both IL-6 and its soluble receptor are expressed in breast tumours[74] and IL-6 levels are higher in women with breast cancer.[75] IL-8 and its receptors are over-expressed in breast cancer and through regulation of MMP-2 activity, IL-8 may also play a role in the invasiveness of breast cancer.[76] Finally, IL-10, a Th-2 immune depressive cytokine, inhibiting the production of interferon-γ and TNF-α, in the human breast, appears to be involved in mammary involution.[77] Although these data suggest that breast cancer involves inflammation, it does not imply that immune reactivity induces breast cancer. The latter is implied by recent findings that the TNF-α –308A polymorphism, associated with increased TNF-α production[78–83] is more frequent in patients with breast cancer[84] and that the TGF-beta1 genotype is associated with an increased risk for breast cancer.[85] Thus, Th-1 upregulation may actually predispose to breast cancer.

4.2. *Inflammation and ovarian cancer*

We have previously suggested that inflammation may also influence the development of ovarian cancer.[7] Bearing children, using oral contraceptives and breastfeeding, which have been shown consistently protect against ovarian cancer, suppress ovulation,[86] a process that involves inflammatory mediators and involves repair of the epithelial wound created by extrusion of the ovum.[87,88] Other established epidemiological risk factors for ovarian cancer, many of which cannot be explained by hormones alone or by ovulation suppression, are also associated with inflammation. These include using talcum powder, a crystal with an asbestos-like structure,[6,89–95] pelvic inflammatory disease,[96,97] and hyperthyroidism.[6] As with breast cancer, the use of anti-inflammatory agents, such as aspirin and NSAIDS, which inhibit mitotic activity in ovarian cancer cell lines[98] appear to protect against the disease.[99–103]

Th-1 cytokines including TNF-α, IL-6, and IL-1α and β are elevated in epithelial ovarian tumours, in ascitic fluid around tumours, or in serum of women with ovarian cancer; the level of TNF-α expression correlates with tumour grade.[104–107] IL-8 is expressed in the normal human ovary where it is also regulated by IL-1[108] IL-8 may inhibit ovarian epithelial apoptosis, predisposing to ovarian cancer.[109–111] Finally, a polarised IL-10 response, albeit a Th-2 cytokine, appears to be produced by ovarian tumours.[112–114] A panel of serum markers, including IL-6, IL-8 and VEGF and reduced concentrations of EGF and IL-12p40 strongly distinguished women with early stage ovarian cancer from controls.[115] With regard to predisposition to ovarian cancer, the IL-1RN gene has a penta-allelic 86-bp tandem repeat (VNTR) in intron 2, of which the less common allele 2 has generally been associated with a reduction in expression[116–118] and an elevation in auto-immune conditions. In one study, the VNTR*2 allele was associated with a 2.7-fold elevated risk for ovarian cancer.[119] Moreover, in a nude mouse model, treatment of ascitic ovarian cancer with TNF-α promoted solid tumour nodule formation, and over-expression of TNF-α conferred invasive properties on some tumour cell lines.[3,120]

5. Hormones in breast and ovarian cancer

Oestrogens, progesterone and androgens are all believed to contribute to breast cancer development, especially in post-menopausal women[121–126] Early menarche, late menopause and length of reproductive life, factors consistent with prolonged exposure to endogenous oestrogens, have consistently been associated with an increased risk of breast cancer in post-menopausal women.[127] In older post-menopausal women, serum concentrations of oestradiol predict the risk of breast cancer: in a recent pooled analysis of nine prospective studies[128] a single measurement in the highest, compared with the lowest quintile of free oestradiol doubled the risk for developing post-menopausal breast cancer (RR 2.58, 1.76–3.78). Body mass index (BMI), which increases oestrogen levels in post-menopausal women,[129] elevates the risk for breast cancer by about 3% per kg/m^2.[130] Moreover, bone mineral density, an integrated marker of long-term oestrogen exposure, is positively associated with breast cancer risk.[131,132] Hormone therapy (HT), the primary source of exogenous oestrogen in post-menopausal women, may increase the risk of breast cancer.[133] However, recent data from the Women's Health Initiative randomised clinical trial suggested that this increase is associated only with oestrogen + progestin formulations; women on oestrogen-only formulations do not appear to have an increase in breast cancer incidence (HR 0.77, 95% CI 0.59–1.01).[134] These data, together with previous data showing a modest increase in breast cancer risk with oestrogen alone, but a greater risk for oestrogen plus progestin,[135] suggest that progestins may enhance breast cancer risk, an observation consistent with the fact that maximum mitotic activity in breast tissue coincides with maximum progesterone levels during the luteal phase of the menstrual cycle.[136]

Elevated serum or urinary androgen levels have also been associated with the development of post-menopausal breast cancer in at least seven cohort studies.[124–126,137–140] Two cohort studies did not show an association,[141,142] but both were small (n = 15 and 39 cases, respectively) and one involved pre-menopausal women.[141,142] A pooled analysis of cohort studies estimated that the relative risk of breast cancer in women with testosterone in the top as compared with the bottom quintile was 2.2 (95% CI 1.6–3.1) and that the dose–response relationship between testosterone and breast cancer risk was statistically significant.[143] Two of the cohort studies showed a correlation with free testosterone, the measure of bioavailable testosterone. Moreover, several case-control studies have shown that women with breast cancer have elevated levels of testosterone.[144,145] Thus, consistently, observational data have linked plasma testosterone levels to breast cancer risk.

Ovarian cancer risk may also be influenced by sex steroid hormones, specifically unopposed oestrogens and androgens. Pregnancy and oral contraceptive use, both markedly protective against ovarian cancer[89,146–165] are associated with a reduction in lifetime exposure to unopposed oestrogens (since both involve oestrogen + progesterone)[166,167] whereas, early menarche and late menopause increase ovarian cancer risk. Moreover, progestin-only oral contraceptives, which do not totally suppress ovulation, are as protective against ovarian cancer as oestrogen-progestin formulas.[168] Finally, HT increases the risk of ovarian cancer[169,170] and in one study, this risk was limited to formulations involving oestrogen alone or sequential oestrogen + progestin (wherein most of the month involves ingestion of oestrogen alone).[171]

Elevated androgen levels may also play a role in ovarian cancer. Androgens are produced by ovarian theca cells, are present in follicular fluid, and are the principal sex steroid of growing ovarian follicles[172] Moreover, the post-menopausal ovary is androgenic[173] and androgen receptors are found in normal ovaries,[174] further supporting the activity of androgens within the organ. In addition, oral contraceptives suppress ovarian testosterone production by 35–70%.[175–179] A prospective study[180] found significantly higher levels of androstenedione in the serum of cases compared with controls, and polycystic ovarian syndrome (PCOS), a condition that elevates androgens[181–183] is associated with ovarian cancer.[184] Finally, androgenic agents used to treat endometriosis may increase ovarian cancer risk[185] It is unclear whether androgen directly impacts ovarian cancer risk, or whether the excess risk involves androgen conversion to oestrogen via aromatase.

Thus, sex hormones appear to play a role in the development of breast and ovarian cancers, although the specific hormone–disease relationships differ by cancer type. In particular, although androgens and oestrogen appear to be involved in both cancers, progesterone may be mitogenic in the breast and protective in the ovary.

6. Endometriosis: interaction between inflammation and hormones

Altered immune function in women with endometriosis is ubiquitous, may favour the growth and progression of endometriosis, and upregulates local oestrogen, a major driver of endometriosis. Sites of endometriosis are surrounded by peritoneal inflammatory cells,[186–188] but rather than clearing the ectopic endometrium, these cells (e.g., natural killer (NK) cells) express reduced cytotoxicity.[189–191] Resection of endometriotic foci increased the percentage of moderately differentiated NK cells, suggesting that endometriosis disturbs differentiation of NK cells.[192] Peripheral and peritoneal T-cells and macrophages are also increased and activated in women affected by endometriosis,[193–197] yet they do not clear endometriotic foci, presumably because of aberrant cytokine and growth factor production.[198] For example, high levels of peritoneal TGF-β, typically found in the peritoneal fluid surrounding implants, inhibits NK activity around endometriosis.[199] Moreover, with the exception of high levels of TNF-α, Th-2 cytokines dominate the peritoneal environment and Th-1 cytokines dominate the internal endometriosis environment.[186,200–203] Peritoneal macrophages also produce MMP-9 and VEGF, vascular permeability and angiogenesis factors that may enhance the vascular support for ectopic endometrium.[204–206]

B cell function and antibody production also appear to be abnormal in endometriosis. Indeed, endometriosis has several of the characteristics of an auto-immune disease.[188,207] In a recent study of more than 3600 volunteers with surgically verified endometriosis, rates of reported Sjogren's syndrome were 24 times that expected in the general population, rates of systemic lupus erythematosus were 20 times higher than

expected, and thyroiditis was six times higher than expected.[208] Biological features characteristic of auto-immune disease that are found in endometriosis include: T and B lymphocyte aberrancies, multiple organ tissue damage, polyclonal B lymphocyte activation, and altered apoptosis.[187,207,209–211] These aberrancies may help ectopic endometrium to escape destruction. Treatments which shrink foci, such as Danazol or GnRH agonists, return depressed levels of apoptosis and elevated levels of auto-antibodies to normal.[212–214] In combination, these observations suggest that 'successful' endometriosis uses the immune system to favour its own growth and invasion by manufacturing cytokines and growth factors as well as potentially co-opting host immune defences.

Endometriosis appears to be a condition stimulated by oestrogens and inhibited by progesterone. Women are most likely to acquire the condition in their reproductive years. Many markers of excess unopposed oestrogen tend to elevate the occurrence of endometriosis.[215] Notably, these risk factors overlap with those for ovarian cancer and breast cancer. They include early menarche[216–220] short or long menstrual cycle[216–218,221,222] and tall stature.[184] Pregnancy[223–225] and oral contraceptive use[216,218,222,226] may reduce endometriosis risk. These relationships are difficult to deconstruct, however, because oral contraceptives are a staple of treatment for endometriosis, and endometriosis causes infertility. More direct evidence relating oestrogens to endometriosis comes from an autopsy study of 399 rhesus monkeys,[227] 20% of whom were serendipitously found at death to have endometriosis. Exposure to oestrogen implants was associated with a 9-fold excess of endometriosis.

The amount of local oestrogen to which endometriotic tissue is exposed probably exceeds systemic levels. This is because ectopic endometrium converts androstenedione to oestrone and oestradiol.[228] In ectopic endometrium, steroidogenic factor-1 (SF-1) a transcription factor capable of stimulating aromatase production, binds more avidly to the aromatase promoter site than does competing binding protein (COUP-TF) a factor that inhibits transcription. Therefore, the aromatase gene is preferentially expressed. In contrast, normal, eutopic endometrium does not express SF-1 and therefore does not produce aromatase.[229] An excess of endogenous androgens might then be expected to drive endometriotic progression. Yet synthetic androgens are used to treat endometriosis. The explanation for this apparent inconsistency may be that exogenous androgens downregulate pituitary gonadotrophins and thus oestrogen production. The overall effect of exogenous androgens may thus be to reduce oestrogenic stimulation of endometriotic foci.

Further autocrine exposure to oestrogen is accomplished by the synthesis of oestrone to oestradiol by ectopic endometrium. Oestradiol is substantially more potent than oestrone. Its conversion from oestrone is accomplished by the enzyme 17β-HSD type 1.[230,231] The converse situation: conversion to oestrone from oestradiol, is accomplished by transcription of a separate gene, producing the enzyme 17β-HSD type 2.[232–234] In ectopic endometrium, expression of 17β-HSD type 2 is absent.[235] Thus, ectopic endometrium synthesises oestradiol, the more potent form of oestrogen, without having any mechanism to convert it back to oestrone. In normal endometrium, glandular cells express large amounts of 17β-HSD type 2, induced by progesterone. Although endometriotic foci are resistant to the anti-oestrogenic effects of progesterone, the fact that progestins are a standard and effective treatment modality for endometriosis suggests that this resistance can be overcome.

A central activity of oestradiol in enlarging endometriotic foci appears to be that it promotes MMP expression.[236–239] Moreover, oestrogen induces COX-2, which gives rise to increased concentrations of prostaglandin (PGE_2).[229] Furthermore, PGE_2 stimulates aromatase, the enzyme that converts androstenedione to oestrone and oestradiol.[240] This interplay between PGE_2 and aromatase creates a positive feedback loop within ectopic endometrium, resulting in local elevations in both pro-inflammatory prostaglandins and oestrogens[228,240,241] Thus, endometriotic foci enrich the oestrogen in their local environment, both through conversion of systemic androstenedione to oestrone and oestrone to oestradiol and through aromatase, 17β -HSD type 1, but also through stimulation of PGE_2. That is, in endometriosis, a relatively well-understood inflammatory-hormonal escalation promotes tumour development.

7. Sex hormones and inflammation in relation to breast and ovary cancer

Inflammatory mediators have emerged as important regulators of oestrogen synthesis in breast tissue as well. IL-6 levels increase the activity of aromatase in breast and adipose tissue, thereby directly increasing systemic and local breast oestrogen levels.[242] Within the breast, TNF-α can also act alone[243] or synergistically with IL-6 to enhance the activities of aromatase[244] E2DH[245,246] and oestrone sulphatase[247] the three enzymes involved in the production of oestradiol from androstenedione, oestrone and oestrone sulphate, respectively. IL-1α levels inversely correlate with local sex steroid receptor expression[248] suggesting an interplay between the cytokine and steroid hormones within breast cancer cells.[249] Finally, IL-8 influences the activity of 17-HSD, enhancing oestrogenic activity.[250]

Conversely, sex steroid hormones directly affect cytokines.[251] For example, oestrogen receptor complexes can bind directly to the IL-6 promoter region,[252] resulting in decreased IL-6 promoter activity. In addition, expression of many cytokines and growth factors is menstrual cycle dependent[253] and hormone therapy (HT) may impact the expression of several cytokines, including IL-2, IL-6, TNF-α and IFN-γ[254–257] 2-MeOE2, a metabolite of oestradiol associated with reduced risk of breast cancer,[122] inhibits the production and actions of both IL-6 and TNF-α.[258,259]

8. Cytokines and hormones interact in the ovary

There is also mounting evidence of hormone–cytokine interactions within the ovary. For example, ovulation involves increased production of TNF-α, IL-1β, IL-6 and COX-2.[260–262] Indeed, the anti-inflammatory NSAIDs inhibit human ovulation.[263] Ovarian cancers are thought to arise within inclusion cysts, epithelium that folds into the stroma as surface cells

are entrapped in the ovarian wound created during ovulation. This brings epithelium into close proximity with stromal inflammatory mediators involved in ovulation.[1,88,261,264] Steroid hormones in the ovarian stroma and epithelium modulate both Th-1 cytokines and TGF-β expression.[265,266] Finally, cytokines and growth factors including IL-1, IFN-γ, TNF-α and IGF-1 directly stimulate ovarian steroidogenesis[267–269] and may play a role in both ovulation and oestrogen-induced tumour growth.[251]

Hence, as in endometriosis, in both the ovary and breast, there appears to be an interaction between sex steroid hormones and cytokines/growth factors. It can be readily postulated that the mutual upregulation of these systems may promote carcinogenesis in both reproductive organs.

9. Summary

Endometriosis is associated with both ovarian and breast cancers. The relationship with ovarian cancer can be understood as a local process of malignant transformation, whereas the relationship with breast cancer cannot. Sex steroid hormones and inflammation have been implicated in the pathogenesis of each of endometriosis, ovarian cancer and breast cancer. A possible explanation for the association between endometriosis and these reproductive cancers is one of local and systemic enhancement of aberrant inflammatory and hormonal mediators. In susceptible tissues, i.e., ones wherein inflammatory–hormonal interactions are most influential, the impact of endometriosis may be to promote a feed-forward loop that favours cancer progression.

Several clinical considerations arise from an emerging understanding of how endometriosis might mediate cancers. First, endometriosis may well be considered a risk factor for ovarian and breast cancers, triggering increasingly intensive surveillance and the possible use of chemoprevention in affected women. Secondly, treatments for endometriosis may best take into consideration the impact on long-term cancer risk. For example, increasing circulating steroid hormones may be harmful long-term, whereas modulation of inflammatory balance may be beneficial. Thirdly, the evolving basic science that characterises how hormones and inflammatory mediators interact within endometriotic implants may have relevance beyond endometriosis. Other cancers, such as prostate, colon and endometrial, may involve hormone-inflammatory interactions. Finally, the notion that a nidus of inflammation in one tissue could have effects on a distant tissue may have extensive implications on other inflammation–cancer relationships.

Conflict of interest statement

None declared.

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