*Hypothesis/Commentary*

# Inflammation and Endometrial Cancer: A Hypothesis

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## Abstract

**Endometrial cancer is the most common gynecologic malignancy in the United States. Substantial epidemiologic data implicate an imbalance of estrogens and progestogens in the etiology of this disease. We propose that inflammation also plays a role in endometrial cancer development. Emerging laboratory data suggest that elevated levels of prostaglandin $E_2$ may underlie the transformation of normal endometrium to neoplastic tissue and that *in vitro* nonsteroidal anti-inflammatory drugs may inhibit endometrial cancer cell growth. In this review, we suggest that the risk factors for endometrial cancer—unopposed estrogens, anovulation, polycystic ovary syndrome, excessive menstruation, early menarche, and late menopause—may be viewed as factors increasing the exposure of the endometrium to inflammation, whereas pregnancy and smoking, two likely protective factors, have the opposite effect. Chronic inflammation can induce rapid cell division, increasing the possibility for replication error, ineffective DNA repair, and subsequent mutations. A proinflammatory milieu can also directly increase estrogen production. Hence, inflammation may work in conjunction with or in addition to estrogen exposure in the development of endometrial cancer.** (Cancer Epidemiol Biomarkers Prev 2005;14(12):2840–7)

## Introduction

Substantial epidemiologic data implicate an imbalance of estrogens and progestogens in the etiology of endometrial cancer (Table 1): early menarche (1, 2), late menopause (3, 4), anovulation (5, 6), prolonged menstruation, obesity (7-9), polycystic ovary syndrome (10), and diabetes mellitus (11-13), characteristics or conditions involving a relative increase in exposure to endogenous estrogens, have been associated with an increased risk of the disease. All three prospective studies that have examined hormone levels observed an increase in endometrial cancer risk with increasing circulating levels of estrogen (14-16). Unopposed estrogen therapy (17-19) and tamoxifen (20, 21), both of which exert proliferative effects on the endometrium, have also been associated with an elevated incidence of the disease. Conversely, increased parity (4, 11, 22, 23) and combination oral contraceptive use (4, 24-26), both characterized by a relatively high degree of exposure to progestogens, are associated with reduced risk of endometrial cancer. Exposure to endogenous or exogenous estrogens not adequately opposed by progestogens leads to an increase in the mitotic activity of endometrial epithelial cells (27). This excessive activity results in increased DNA replication and repair errors, which, in turn, can lead to somatic mutations that may ultimately give rise to endometrial hyperplasia and subsequent malignancy. In this review, we propose that inflammation may work in conjunction with or in addition to estrogen exposure in the development of endometrial cancer (Fig. 1). Support for our hypothesis comes from several observations, including the fact that the effect of the menstrual cycle resembles an inflammatory process, that unopposed estrogens have an inflammatory effect on the endometrium, and that many of the established risk factors for endometrial cancer can be viewed as producing inflammation in the endometrium. This proinflammatory milieu can initiate and promote neoplastic transformation directly. It can also increase estrogen production, which may facilitate carcinogenesis by disrupting the estrogen-progestogen balance.

## The Inflammation-Cancer Link

Epidemiologic studies have documented a relationship between local tissue inflammation and cancer development at that site. Examples include hepatitis and liver cancer (28) and colitis and colon cancer (29). The inverse association between long-term use of nonsteroidal anti-inflammatory drugs (NSAID) and reduced risk of several cancers (30-34) further supports an inflammation-cancer link. Although the means by which local inflammation facilitates cancer development is unknown, inflammatory cells and, in particular, the production of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), by both local tissue and infiltrating inflammatory cells, seem to play a key role (reviewed in refs. 35-40). These inflammatory cells induce rapid cell division and produce increased concentrations of free radicals (41) that may subsequently damage DNA. Increased rates of cell turnover are associated with a greater likelihood of replication errors and ineffective DNA repair at key regulatory sites, such as within tumor suppressor genes, which may increase the probability of converting DNA lesions to mutations (42). Moreover, inflammatory cytokines induce a range of inflammatory enzymes, including cyclooxygenase-2 (COX-2). COX-2 cyclizes and oxygenates arachidonic acid, eventually producing prostaglandin $E_2$ ($PGE_2$; ref. 43). $PGE_2$ can facilitate tumorigenesis by increasing production of cytokines and growth factors necessary for tumor growth, invasion, and metastases, including interleukin (IL)-6, IL-8, vascular endothelial growth factor, and matrix metalloproteases (44). $PGE_2$ also increases production of inducible nitric oxide

Received 7/6/05; revised 9/19/05; accepted 9/27/05

**Grant support:** National Cancer Institute grant K07-CA80668.

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doi:10.1158/1055-9965.EPI-05-0493

**Table 1. Risk factors for endometrial cancer in relation to the estrogen/progestogen imbalance hypothesis and the proposed inflammation hypothesis**

| Risk/protective factor | Proposed mechanism—estrogen/progestogen imbalance hypothesis* | Proposed mechanism—inflammation hypothesis |
|---|---|---|
| Risk factors | | |
| Unopposed estrogen therapy use | Unopposed estrogen exposure in the endometrium | Increased exposure to estrogens increases inflammatory response in the endometrium |
| Obesity | Increased systemic exposure to unopposed estrogens via aromatization of androgens in adipose tissue and via decreased sex hormone–binding globulin production<br>Decreased progesterone exposure leading to unopposed estrogen exposure due to anovulation | Increased proinflammatory systemic milieu |
| Diabetes mellitus | ? | Increased proinflammatory systemic milieu |
| Polycystic ovary syndrome | Increased systemic exposure to unopposed estrogens via aromatization of androgens | Increased proinflammatory systemic milieu |
| Early menarche/late menopause | Increased lifetime exposure to estrogen in the endometrium | Increased lifetime exposure to inflammation via increased number of menstruations |
| Anovulation | Decreased progesterone production leading to unopposed estrogen exposure in the endometrium | Decreased exposure to progesterone increases inflammatory response in endometrium |
| Menorrhagia | ? | Increased exposure to inflammation via menstruation |
| Protective factors | | |
| Pregnancy | Increased exposure to progesterone | Decreases exposure to menstruation<br>Increased exposure to anti-inflammatory effect of progesterone<br>Decreased inflammatory milieu in the uterus |
| Smoking | Decreased exposure to estrogens due to increased metabolic clearance and production of less estrogenic metabolites | Production of anti-inflammatory estrogen metabolite |
| Oral contraceptive use | Increased exposure to progestins | Increased exposure to anti-inflammatory progestins<br>Decreased exposure to menstruation |

*Adapted from ref. 145.

synthetase, an enzyme involved in free radical generation (44). Further evidence for a role of COX-2 in cancer formation comes from the observation that carcinogenesis is inhibited in mice treated with COX-2-selective inhibitors and in COX-2 knockout mice (45, 46). Hence, neoplastic transformation may be initiated by DNA damage incurred by cells as a result of free radical generation. These initiated cells may be further promoted via COX-2-mediated up-regulation of $PGE_2$, which causes the production of factors supporting growth, invasion, and metastases.

More recently, laboratory data suggest that the molecular pathway underlying the cancer inflammation association involves the nuclear factor-κB (NF-κB) transcription factor and its inhibitor κB kinase (IKK) complex. NF-κB is a transcription factor that regulates apoptosis, cell proliferation, and cell growth arrest, as well as enhances angiogenesis via vascular endothelial growth factor expression (47). The NF-κB pathway is also a crucial second messenger system for inflammatory cytokine signaling (48). In most normal cells, NF-κB remains in the cytoplasm and is inactive until the cell is stimulated by an appropriate ligand (47). One group of activators of NF-κB are the proinflammatory cytokines, including TNF-α and IL-1β, which after complexing to their receptors recruit kinases that activate the IKK complex. The activated IKK complex phosphorylates IκB, the inhibitory chaperone molecule bound to NF-κB. NF-κB is then liberated and translocated to the nucleus, where it activates a variety of genes, including those involved in inflammation and proliferation (49). Constitutive IKK activity resulting in altered NF-κB activation is a hallmark for inflammatory diseases (50). Liberated NF-κB protein may also activate malignancy-promoting signaling pathways in both cancer cells and tumor-associated inflammatory cells (51), and aberrant NF-κB activity has been reported for several cancers, including estrogen-associated breast cancer (52, 53). Recently, animal models have further elucidated the role of NF-κB in tumorigenesis. In an inflammation-associated murine model of liver cancer, TNF-α produced by adjacent stromal cells activated NF-κB in hepatocytes undergoing malignant transformation (54). Inhibition of TNF-α in the stromal cells subsequently induced hepatocyte apoptosis, thereby reducing tumor formation. Moreover, in an inflammation-associated model of colon cancer, deletion of IKK-B in intestinal epithelial cells increased apoptosis, thereby reducing the development of intestinal tumors, although IKK-B deletion did not decrease epithelial inflammation (54). In addition, selective deletion of IKK-B from inflammatory infiltrates in malignant and premalignant tumors resulted in decreased proinflammatory cytokine expression within the infiltrates as well as reduced tumor formation. Together, these data suggest that the NF-κB pathway invoked by proinflammatory cytokines may be involved in tumor promotion by inhibiting apoptosis in initiated cells as well as by further stimulating production of proinflammatory cytokines by myeloid and lymphoid cells within the tumor mass. These proinflammatory cells can then feed back into the NF-κB pathway, further promoting the proliferative, antiapoptotic, and proinflammatory process (51).

Thus, chronic inflammation with its subsequent generation of free radicals and up-regulation of COX-2 can lead to a cascade of events that may eventually initiate malignant transformation. Initiated cells can be further promoted by NF-κB proteins freed as a result of up-regulated proinflammatory cytokines. Activated NF-κB both inhibits apoptosis and stimulates production of proinflammatory cytokines, which can further promote proliferation of initiated cells. Hence, tissue exposed to chronic inflammation or to a proinflammatory milieu may be more susceptible to the carcinogenic process.

**The Human Endometrium and the Menstrual Cycle: Shared Features with a Chronic Inflammatory Process.** The human endometrium consists of glandular and surface epithelia, a surrounding stroma, and a vascular system found only in menstruating species (55). Throughout the childbearing years, the endometrium undergoes cycles of rapid growth, remodeling, differentiation, and angiogenesis. These changes are directly and indirectly caused by steroid hormones and are the result of cytokines synthesized and released by the epithelial, stromal, and vascular cells of the endometrium (56). During the menstrual cycle, the endometrium goes through the proliferative phase, marked by an increase in endometrial thickness; the secretory phase, characterized by the development of spiral arteries and stromal edema after ovulation; and the menstrual phase, marked by the shedding of the endometrial lining. During the three phases, steroid hormone levels vary. Estradiol increases and reaches its peak during the mid-proliferative phase. There is another, smaller increase and peak in estradiol during the midsecretory phase. Progesterone levels are extremely low during the menstrual and early proliferative phases, begin to increase toward the end of the proliferative phase, and peak during the midsecretory phase (57).

The menstrual phase of the endometrium includes inflammation as a physiologic component. Thus, in the absence of a pregnancy, the endometrium can be viewed as being cyclically exposed to a chronic inflammatory-like process. Inflammation is the response of the body to tissue damage resulting from a physical, chemical, or infectious agent, and involves the release of a host of factors, including cytokines, growth factors, and prostaglandins (40). After an insult, thrombi are formed, polynuclear and later mononuclear cells are recruited, fibroblasts proliferate, angiogenesis occurs, and collagen is deposited. The granulation tissue is gradually replaced by a scar and the epithelial tissue is repaired. A similar ''injury'' scene with its resulting cascade of inflammatory events occurs during the endometrial cycle. During the late endometrial secretory phase, there is a loss of integrity of the lysosomes and acid hydrolases are released, leading to tissue damage including autodigestion of several cell components, including the membrane (58). The resulting injury causes platelets to amass, thrombi to form, and prostaglandins to be released (59). During this period, ischemic necrosis due to contraction of the endometrial vessels occurs and stromal granulocytes infiltrate the endometrium, reaching a peak during the menstrual phase (60). The vasoconstriction-vasodilation cycles and resulting hypoxia releases a plethora of reactive oxidative species resulting in a degradation of IκB proteins (61) and activation of NF-κB (62, 63). NF-κB induces COX-2, prostaglandin, and inflammatory cytokine release (56), a response that ultimately leads to menstruation (61). Endometrial damage is most apparent during the early menstrual phase when the epithelial and surrounding stroma are detached from the underlying basal layer (60) leaving a thin, denuded endometrium that retains the basal layer and a small portion of the surface epithelium. Migration and proliferation of these epithelial cells, together with angiogenesis of the arterial stumps left in the basal layer, are the main means of endometrial surface repair.

Given the inflammatory component of menstruation (64), it is not surprising that menstruation involves the synthesis and release of inflammatory factors, including cytokines, growth factors, COX-2, and prostaglandins (56, 60, 65), as well as activation of NF-κB (63). Conceivably, these factors could bear on the initiation and progression of endometrial malignancies (66, 67).

**Endometrial Cancer Risk Factors Are Associated with a Proinflammatory Milieu.** Host factors as well as lifestyle factors play a role in cytokine expression and, hence, can influence the inflammatory nature of the local and systemic milieu. For example, systemic IL-6 and TNF-α levels increase with age (68, 69) and body mass index (70, 71). Indeed, evidence suggests that obesity, a strong risk factor for endometrial cancer, may be a systemic inflammatory condition (72). In addition to elevated serum levels of IL-6 and TNF-α, healthy obese individuals have elevated circulating levels of C-reactive protein, leptin, and macrophage migration inhibitory factor, three markers of inflammation (73, 74). These elevated circulating levels are attributed to increased production of these and other proinflammatory proteins within adipose tissue, and, in the case of C-reactive protein, within the liver as a result of increased expression of IL-6 by adipocytes (75). Thus, proinflammatory cytokines secreted by adipose tissue modulate the immune system in favor of a state characterized by chronic low-level systemic inflammation (76). Given the high population attributable risk for endometrial cancer associated with excess adiposity [~56.8% in the

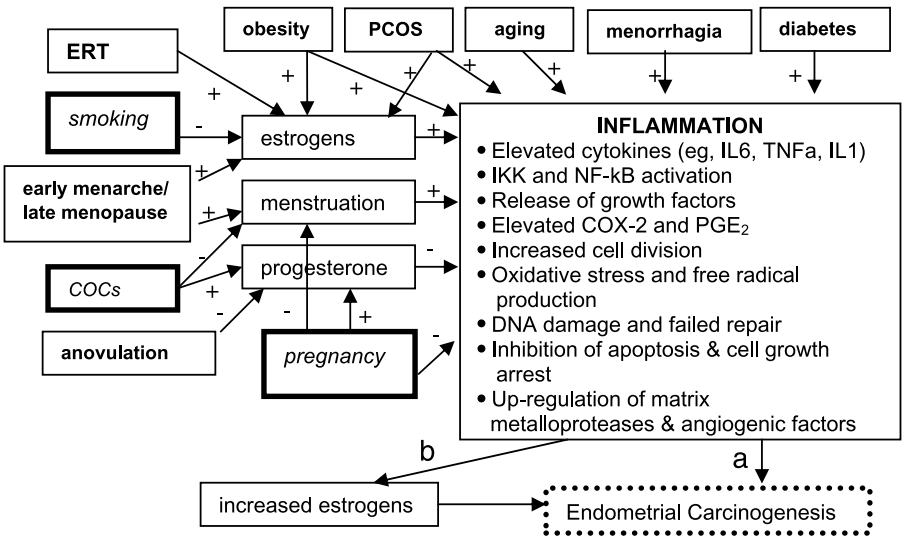


**Figure 1.** Proposed relationships among endometrial cancer risk/protective factors, inflammation, and endometrial carcinogenesis. Endometrial cancer risk factors (*in bold*) either influence inflammation directly or influence factors that increase inflammation (estrogen, menstruation) or decrease inflammation (progesterone). Protective factors (*in italics*) exert the opposite effects. The effects of inflammation can cause mutagenesis, ultimately leading to endometrial carcinogenesis either directly (**a**) or indirectly (**b**) by increasing estrogen levels. *ERT,* unopposed estrogen therapy; *COC,* combined oral contraceptives; *PCOS,* polycystic ovary syndrome.

United States and 45.2% in Europe (77) for body mass index >25.0 kg/m$^2$], it is important to evaluate the means by which obesity exerts its detrimental influence. There is also mounting evidence that diseases involving insulin insensitivity that are associated with endometrial cancer, such as diabetes, also show increased proinflammatory cytokine production, especially IL-1, IL-6, and TNF-α (78, 79). TNF-α is also increased in women with polycystic ovary syndrome, with the effect being most notable in lean women (80). Notably, this proinflammatory milieu associated with endometrial cancer risk factors may increase estrogen production (81).

Estrogen metabolism may also affect cytokine expression. In the liver, estrogens are predominantly metabolized via either the 2-hydroxylation or 16α-hydroxylation pathways (82). In the uterus, 4-hydroxylation of estradiol has also been observed (83). Because these enzymes compete for a limited substrate pool, an increase in one pathway will reduce the amount of product in the competing pathway. Host factors, such as weight (84), as well as lifestyle factors, such as cigarette smoking (85), influence which pathway predominates. Greater weight is associated with a shift to the 16α-hydroxylation pathway, whereas cigarette smoking, a putative protective factor (86), is associated with a shift to the 2-hydroxylation pathway. Notably, 2-hydroxyestradiol and its methoxy derivative do not possess uterotropic activity, whereas both the 4-hydroxylation and 16α-hydroxylation metabolites are potent estrogens with uterine activity (87). Moreover, 2-methoxy-estradiol (an *O*-methylated product of 2-hydroxylation) seems to inhibit tumor growth, induce apoptosis, and alter microtubule stability (88). It also acts to inhibit the production and actions of both IL-6 and TNF-α (88, 89). Hence, the protective effect of smoking or the increased risk associated with obesity may result from the shift in estrogen metabolism, which exerts a direct effect on proinflammatory cytokines. Finally, whereas embryo implantation evokes an inflammatory response (90), pregnancy is associated with a temporary shift in the cytokine pattern to an anti-inflammatory endometrial milieu (91, 92). In particular, the first trimester decidua is characterized by an increase in IκBα, the inhibitory chaperone molecule for NF-κB (63).

Hence, factors associated with endometrial cancer risk, such as obesity and diabetes, also favor the production of proinflammatory cytokines. In contrast, factors associated with reduced risk, such as smoking and pregnancy, favor an anti-inflammatory milieu.

**Interrelationship of Sex Hormones with Cytokines and Growth Factors in the Endometrium.** Estrogen and progesterone are the well-established regulators of the human endometrium. However, less clear is whether this regulation is through direct interaction with endometrial epithelial cells or indirectly through interaction with stromal and vascular cells (93, 94). Emerging data suggest that estrogen and progesterone exert their effects by influencing the production of cytokines and growth factors found in the endometrium (56, 95), which act on the endometrium as well as the stromal and perivascular cells (93). For example, expression of many cytokines and growth factors in the endometrium is menstrual cycle dependent: Epidermal growth factor, insulin-like growth factor-I, and transforming growth factor-β and their receptors are most highly expressed in the proliferative phase, whereas IL-1, IL-6, and TNF-α are most highly expressed during the secretory and menstrual phases (96, 97). Estrogen directly regulates the endometrial production of many of these cytokines and growth factors as well as their receptors (95, 98, 99).

Progesterone also influences cytokine, growth factor, and prostaglandin production in the endometrium. The ingress of platelets during the proliferative phase of the human endometrium leads to an increase in prostaglandins, which further stimulates platelet ingress (93). This spiraling inflammatory response is blunted by the sudden increase in progesterone produced by the corpus luteum after ovulation (93). Specifically, progesterone stimulates production of prostaglandin dehydrogenase (100), thereby facilitating the breakdown of prostaglandins. Progestins can also inhibit cytokine-induced transcription of COX-2 (101). In addition, during the proliferative phase of the endometrium, NF-κB is activated (102) and its resulting inflammatory, proliferative, and antiapoptotic effects are inhibited by progesterone and its receptor (103). The observation that a strong uterine inflammation occurs in knockout mice lacking a progesterone receptor further supports the anti-inflammatory effects of progesterone in the endometrium (104). Thus, natural menstrual cycles lacking an ovulation or an endometrium that is exposed only to unopposed estrogens would be characterized by an inflammatory milieu. As discussed, this proinflammatory milieu may directly facilitate carcinogenesis. Moreover, it can also increase estrogen production (81). In particular, IL-6 can stimulate estrogen synthesis and can act synergistically with TNF-α to enhance the activities of aromatase (105), 17β-hydroxysteroid dehydrogenase (106, 107), and estrone sulfatase (108), the three enzymes involved in the production of estradiol from androstenedione, estrone, and estone sulfate, respectively. Thus, a proinflammatory milieu can also contribute to an estrogen-progestogen imbalance, possibly predisposing the endometrium to the neoplastic process.

Hence, there is a complex interaction between sex steroid hormones and cytokine/growth factors within the endometrium. In particular, the absence of progesterone can lead to an inflammatory milieu, which can both increase estrogen production and further induce proinflammatory cytokines, thereby potentially creating an environment susceptible to tumor initiation and promotion.

**Evidence Linking Inflammation and Endometrial Cancer.** In addition to the circumstantial evidence linking inflammation and endometrial cancer just described, emerging laboratory data suggest a link as well. Studies on excised human tissue show that members of the NF-κB family are expressed in the proliferating endometrium, in endometrial hyperplasia, and in endometrial carcinoma (102). Notably, a decrease in NF-κB expression coincides with an increase in apoptosis in low-grade carcinomas, suggesting that up-regulation of NF-κB may prevent apoptosis in endometrial hyperplasia and in early carcinoma (102). Moreover, NF-κB factors are aberrantly expressed in the nuclei of a majority of endometrial cancer tumors, with a strong association between the two components of the heterodimer that characterizes the ''classic form'' of NF-κB (109). This same classic form has been frequently reported to localize in the nucleus of breast cancer cell lines and some breast tumors (110, 111).

Besides its role as a transcription factor for cell survival and proinflammatory genes, NF-κB and its inhibitor IκB seem to regulate expression of COX-2 in endometrial cancer cells (112). In malignant endometrial epithelial cells, NF-κB induces COX-2, which ultimately leads to enhanced production of $PGE_2$ and COX-2 in both the malignant cells and in adjacent endometrial stromal cells (113). Up-regulation of COX-2 is found in many cancers, including endometrial cancer, where its expression seems related to tumor aggressiveness (114). Both NF-κB and COX-2 are expressed in endometrial cancer and during the proliferative phase of the endometrium (102, 115-117). In particular, endometrial explant cultures show that 17β-estradiol up-regulates COX-2 expression during the early proliferative phase of the endometrium (118) and it is the surge in progesterone as a result of ovulation that may up-regulate IκB, the inhibitory chaperone molecule for NF-κB (63), as well as down regulate COX-2 expression (93, 101, 119-121). Consistent with these observations, COX-2 is not found in the secretory phase of the endometrium in women who have ovulated (115) nor in the endometrium of postmenopausal

women using a combined estrogen + progestin hormone therapy regimen (122). Hence, a natural menstrual cycle lacking an ovulation and thus a progesterone surge (and possibly a hormone therapy regimen lacking progestin) would not inactivate NF-κB nor down-regulate COX-2, leaving the endometrium exposed to greater levels of COX-2 enzyme and subsequently $PGE_2$.

COX-2 and $PGE_2$ are also elevated in uterine tissue of women with menorrhagia (excessive menstruation), a known risk factor for endometrial cancer (123). $PGE_2$ is also commonly elevated in malignant endometrial epithelial cells (113). Moreover, elevated $PGE_2$ levels caused by COX-2 up-regulation may underlie the transformation of normal endometrium to neoplastic tissue (66). In particular, within the endometrium, elevated COX-2 and $PGE_2$ can facilitate angiogenesis (124), increase cell proliferation (125), decrease apoptosis (125), inhibit B- and T-cell proliferation and macrophage function (thereby allowing defective cells to proliferate undetected by the immune system; ref. 126) and facilitate tissue invasion (127).

Aspirin has been shown *in vitro* to inhibit endometrial cancer cell growth through the induction of apoptosis in a dose-dependent manner (128). Other NSAIDs have also been shown to reduce endometrial cancer cell proliferation and induce apoptosis in a dose- and time-dependent manner (129, 130). Consistent with data from colon (131) and other cancer cell lines, these laboratory experiments suggest that NSAIDs exert their anticancer effects through both COX-2-dependent and COX-2-independent mechanisms (129). This latter observation suggests that if NSAIDs do protect against endometrial cancer, there may be several underlying mechanisms by which they exert their effects, such as by inhibiting aromatase (132), improving insulin signaling (133-138), trapping reactive oxygen species (139), ameliorating hypoxia/reoxygenation in injured tissues (139-141), and inhibiting macrophage expression of TNF-α (142), a proinflammatory cytokine whose expression varies with estrogen levels in the endometrium. Hence, aspirin and other NSAIDs might exert their effects in the endometrium through both inflammation-dependent and inflammation-independent mechanisms.

## Summary and Conclusions

We propose that inflammation may play a role in the genesis of endometrial cancer. In general, chronic local inflammation may predispose to tumor development by generating free radicals and up-regulating COX-2 and $PGE_2$, which in turn can damage DNA and induce cell proliferation, thus initiating and promoting neoplastic transformation. Chronic inflammation can also dysregulate the NF-κB pathway, thereby inhibiting apopotosis, blocking cell cycle arrest, and further stimulating production of proinflammatory cytokines. A proinflammatory milieu can feed back into this production cycle, further facilitating tumorigenesis. As discussed, the endometrial cycle resembles a state of cyclic chronic inflammation and endometrial cancer risk factors are associated with a proinflammatory milieu. In premenopausal women, the estrogen-dominated proliferative phase of the endometrium is characterized by an increase in NF-κB activity and up-regulation of COX-2 and $PGE_2$, which could lead to a spiraling inflammatory response in the absence of progesterone. A similar effect could be expected in the postmenopausal endometrium of women who receive unopposed estrogen therapy. Menstruation is also associated with elevated COX-2 and $PGE_2$ expression, as well as with NF-κB activation. Thus, the consistent epidemiologic risk factors for endometrial cancer—unopposed estrogen use, anovulation, polycystic ovary syndrome, excessive menstruation, early menarche, and late menopause—may be viewed as factors increasing the exposure of the endometrium to inflammation. Moreover, obesity and diabetes, two other conditions also associated with an increased risk, are also characterized by a shift to a proinflammatory milieu. Pregnancy, which is associated with a reduced risk of endometrial cancer, has the effect of minimizing the number of menstrual cycles, and therefore reducing cumulative exposure to inflammation. Pregnancy also induces a temporary shift to an anti-inflammatory milieu and is associated with an inhibition of NF-κB activity. Women who smoke cigarettes have relatively low risk of endometrial cancer, and smoking shifts estrogen metabolism to a pathway that seems to inhibit inflammatory cytokines. Together, these data suggest an inflammation-endometrial cancer link. Further support for our hypothesis derives from laboratory data showing that NSAIDs inhibit endometrial cancer cell growth *in vitro*; that NF-κB activity is increased in the proliferating endometrium, in endometrial hyperplasia, and in endometrial carcinoma; and that elevated levels of COX-2 typically found in the endometrium exposed to unopposed estrogens lead to increases in $PGE_2$, which can initiate and promote the neoplastic process.

There are several ways to test the hypothesis put forth in this article. First, use of anti-inflammatory medications would be expected to reduce the risk of endometrial cancer. To date, no epidemiologic studies have assessed the association between NSAID use and endometrial cancer. Studies in populations of women with substantial exposure to these medications, such as those with connective tissue diseases, can also elucidate any potential relationship as long as the disease does not inflame the endometrium. Cytokine levels and activity may be altered by cytokine gene variations (143, 144). Thus, individual variations in these genes, either alone or in combination with host and lifestyle factors, may affect endometrial cancer risk. Similarly, susceptibility to the effects of inflammation may be modulated by variation in DNA repair genes, such that individuals with more active repair capabilities may be less susceptible to the effects of endometrial inflammation. The prevalence of these genetic variants in women with and without endometrial cancer can be assessed, thereby shedding light on the biological mechanisms underlying endometrial cancer. Finally, animal models can also be used to assess whether suppression of menstruation-associated inflammation by NSAIDs reduces the development of atypical hyperplasia and other markers of endometrial transformation.

## Acknowledgments

We thank Chandra Marriott and Dr. Jeffrey L. Eppinger for their help with the manuscript.

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*Cancer Epidemiol Biomarkers Prev* 2005;14:2840-2847.