

Review

Obesity, Endogenous Hormones, and Endometrial Cancer Risk: A Synthetic Review¹

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Abstract

Endometrial cancer is a disease of the affluent, developed world, where epidemiological studies have shown that ≥40% of its incidence can be attributed to excess body weight. An additional proportion may be because of lack of physical activity. Alterations in endogenous hormone metabolism may provide the main links between endometrial cancer risk, and excess body weight and physical inactivity. Epidemiological studies have shown increased endometrial cancer risks among pre- and postmenopausal women who have elevated plasma androstenedione and testosterone, and among postmenopausal women who have increased levels of estrone and estradiol. Furthermore, there is evidence that chronic hyperinsulinemia is a risk factor.

These relationships can all be interpreted in the light of the “unopposed estrogen” hypothesis, which proposes that endometrial cancer may develop as a result of the mitogenic effects of estrogens, when these are insufficiently counterbalanced by progesterone. In our overall synthesis, we conclude that development of ovarian hyperandrogenism may be a central mechanism relating nutritional lifestyle factors to endometrial cancer risk. In premenopausal women, ovarian hyperandrogenism likely increases risk by inducing chronic anovulation and progesterone deficiency. After the menopause, when progesterone synthesis has ceased altogether, excess weight may continue increasing risk through elevated plasma levels of androgen precursors, increasing estrogen levels through the aromatization of the androgens in adipose tissue. The ovarian androgen excess may be because of an interaction between obesity-related, chronic hyperinsulinemia with genetic factors predisposing to the development of ovarian hyperandrogenism.

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Introduction

Incidence rates of endometrial cancer are up to 10 times higher in Western, industrialized countries than in Asia or rural Africa (1, 2), and changes in incidence rates over time (3), after industrial development (4), or migration from low-risk to high-risk areas (5–7), have shown that endometrial cancer has strong environmental, *i.e.*, nongenetic, risk factors, which are related to the westernization of lifestyle. These environmental risk factors most likely include low level of physical activity and obesity (4, 5, 8, 9). In different studies, obesity has been associated with a 2–5-fold increase in endometrial cancer risk in both pre- and postmenopausal women (10) and has been estimated to account for ~40% of endometrial cancer incidence in affluent societies (11). Whereas in many studies risk rose approximately linearly with increasing Body Mass Index (BMI),³ a few studies showed a threshold effect, with an increase only among obese women with a BMI of ~30 kg/m² or higher (10). It is possible that this threshold effect might apply especially to endometrial cancer risk among young, premenopausal women (12, 13), and that the more linear increase applies to cancers occurring at a more advanced, postmenopausal age; however, data are insufficient to draw a definite conclusion. Besides excess body weight, epidemiological evidence suggests a possible protective effect of regular physical activity (10), but more studies are needed to confirm this and to estimate more precisely the magnitude of effect.

Although the mechanisms are not understood completely, endogenous hormones appear to play an important role in the development of endometrial cancer. Increased endometrial cancer risk has been associated with early menarche and late menopause, suggesting a relationship of risk with greater lifetime exposure to estrogens at premenopausal levels (5). Other hormone-related factors associated with risk are parity and use of exogenous estrogens for oral contraception or postmenopausal replacement therapy (5, 14–17). Furthermore, risk has been related to plasma concentrations of estrogens, progesterone, androgens, SHBG, and insulin (18–21). It is generally thought that excess weight influences endometrial cancer risk through changes in endogenous hormone metabolism (22, 23).

From a histological and molecular pathology perspective, at least two major types of endometrial tumors can be distinguished. Type I tumors are mostly endometrioid carcinomas, represent up to ~80% of endometrial cancers, and are generally associated with endometrial hyperplasia (15, 24). Type II tumors are more often serous papillary, clear cell, or squamous

³ The abbreviations used are: BMI, body mass index; SHBG, sex hormone-binding globulin; IGF, insulin-like growth factor; SOC, sequential oral contraceptives; COC, combined oral contraceptives; POC, progestogen only oral contraceptives; ERT, estrogen only replacement therapy; SEPRT, sequential estrogen-progestin replacement therapy; CEPRT, combined estrogen-progestin replacement therapy; PCOS, polycystic ovary syndrome; LH, luteinizing hormone; IGFBP, insulin-like growth factor binding protein; E₂, estradiol; E₁, estrone; Δ₄-A, Δ₄-androstenedione; T, testosterone.

carcinomas, and generally develop from atrophic endometrial tissue in older women (24–26). Type I carcinomas are associated with mutations in the *ras* proto-oncogene, and in the *PTEN* tumor suppressor gene, and often show microsatellite instability, but do not usually show mutations in the *p53* tumor suppressor gene. By contrast, a majority of type II tumors have *p53* mutations, but almost never have microsatellite instability or *ras* or *PTEN* mutations. Although most epidemiological studies did not distinguish between these two tumor types, and in those studies that did the numbers of type II tumors were usually small, there is some evidence (reviewed in Refs. 15, 24) that endocrine and nutritional lifestyle factors, including obesity, affect the risk of type I but not of type II tumors.

The purpose of this article is to review current knowledge of the relationships among excess weight, endogenous sex hormones, and endometrial cancer risk, and to propose an endocrine model for the etiology of (type I) endometrial tumors. In section 1, we review the major hypotheses and observations concerning the relationships of endometrial cancer risk with endogenous sex steroids, SHBG, and insulin. In section 2, we discuss common metabolic and hormonal consequences of excess weight. In section 3, we attempt an integration of several theories and findings, and discuss pathways through which endocrine alterations might link excess weight to (type I) endometrial cancer development.

Endogenous Hormones, Endometrial Tissue Proliferation, and Endometrial Cancer Risk

The principal mechanism by which hormones and growth factors are thought to influence cancer risk are their regulatory effects on the balance among cell proliferation, differentiation, and apoptosis (27–34). Increased proliferation rates raise the probability that mutations accumulate in proto-oncogenes (which are often genes directly involved in the regulation of the cell cycle) and tumor suppressor genes. Impairment of apoptosis may allow cells that have harbored such mutations to survive and eventually to expand clonally, thus allowing them to accumulate additional mutations until full malignancy is reached. The differentiation of cells, and maintenance of cells in a differentiated state, are thought to protect against tumor development, because highly differentiated cells have reduced proliferative potential (32, 33). Finally, proliferative stimuli may also enhance the growth of established tumors.

The endometrial tissue consists of stroma, glandular, and surface epithelium. These various cell types respond to sex steroids and other hormones in the circulation, and in addition secrete themselves a variety of growth factors, cytokines, and other peptides that act as paracrine and autocrine regulators of proliferation, differentiation, and apoptosis. In the next paragraphs we discuss the relationships of estrogens, progestins, ovarian androgen excess, and insulin with endometrial tissue proliferation and cancer risk.

Estrogens and Progestins. The predominant theory describing the relationship between endogenous steroid hormones and endometrial cancer risk is known as the unopposed estrogen hypothesis (35, 36). This hypothesis proposes that endometrial cancer risk is increased in women who have high plasma bioavailable estrogens and/or low plasma progesterone, so that mitogenic effects of estrogens are insufficiently counterbalanced by progesterone. This theory originated from at least two important observations, namely: (a) increased endometrial proliferation rates during the follicular phase of the menstrual cycle, during which progestin levels are low, whereas E_2 levels are at normal premenopausal concentrations (36, 37); and (b)

increased endometrial cancer risk among women using exogenous estrogens without progestins (14).

During the follicular phase of the menstrual cycle, when the ovaries produce E_2 but virtually no progesterone, epithelial tissue and stromal fibroblasts in the upper two-thirds of the endometrium (“functional” layer) proliferate (this is referred to as the “proliferative phase” of the endometrium). High proliferation rates continue until ovulation, when plasma E_2 levels reach a nadir, and then decline rapidly during the luteal phase of the menstrual cycle, because of the increase in levels of progesterone, which antagonizes the proliferative actions of E_2 . To a large part, the proliferative actions of E_2 on endometrial tissue are mediated by an increase in the local production (mostly by stromal tissue) of IGF-I (38–41). IGF-I mRNA expression in uterine tissue of rats is markedly dependent on E_2 (42, 43), and in humans the IGF-I gene is also expressed primarily during the follicular and early luteal phases of the menstrual cycle (44, 45). Progesterone diminishes estrogenic action in the endometrium by stimulating the local synthesis of 17β -hydroxysteroid dehydrogenase and estrogen sulfo-transferase (46, 47). These enzymes favor the conversion of E_2 into the less potent estrogen E_1 , and into estrogen sulfates that are rapidly excreted from cells and from the body. Furthermore, progesterone provides the key stimulus for endometrial gene expression and synthesis of IGFBP-1, which inhibits IGF-I action in endometrial tissue (48–53). IGFBP-1 is the most abundant IGF-binding protein in the endometrium (it was initially identified as a major secretory protein of decidualized endometrium, and was given the names “placental protein 12” and “ α_1 -progestin-associated endometrial globulin”). In summary, estrogen-induced IGF-I production, in the absence of progesterone-induced IGFBP-1 synthesis, can explain the increased endometrial cell proliferation during the follicular phase of the menstrual cycle compared with the luteal phase (38, 39). During the luteal phase, when progesterone levels increase strongly, the progesterone-induced increase in IGFBP-1 production may be responsible for the strong decrease in endometrial cell proliferation.

Different exogenous hormone formulations, used for postmenopausal replacement or for contraception, have been found to influence endometrial cancer risk.

There are three types of oral contraceptives: SOC, COC, and POC. SOC formulations include estrogen only pills (for up to 16 days), followed by estrogen and progestogen pills. COC pills contain an estrogen and a progestogen, given throughout the monthly cycle (usually for 22 days).

Users of SOC before late 1970s, and specifically of a particular brand (“Oracon”) containing a long-duration, relatively potent estrogen (ethinylestradiol) and a short-duration, weak progestin (dimethisterone) were shown to be at increased risk of endometrial cancer, which led to withdrawal of these formulations from the market (14). Data relating SOC other than Oracon to endometrial cancer risk are very limited and do not allow definite conclusions (14). Use of COC has been shown to decrease risk of endometrial cancer, the protection being stronger with increasing duration of use, and persisting for many years after discontinuation of use (54). Very limited data about the effect of POC on endometrial cancer risk are available, but despite the small numbers, the results of these studies indicate that POC use is associated with reduced risk of endometrial cancer (14, 54). As discussed above, estrogens and progestins may directly influence endometrial cancer risk by altering local IGF-I bioactivity, thus changing the balance between proliferation and apoptosis. In addition, the greater risk in women using SOC may be explained by the fact that oral

estrogens block ovulation and ovarian progesterone synthesis, thus increasing the number of days in which women are exposed to unopposed estrogens. The protective effect of COC can be explained by the fact that this type of contraceptive pill keeps endogenous E_2 levels comparatively low (comparable with the early follicular phase of the menstrual cycle), whereas simultaneously providing a continuous supply of progesterone, for 21–28 days/cycle (*i.e.*, more than during the natural menstrual cycle in nonusers).

In peri- or postmenopausal women, three major types of hormone therapy are used: ERT, SEPRT, and CEPRT. A meta-analysis of 30 studies showed >2-fold increase in endometrial cancer risk for ever-users of ERT compared with nonusers, and a rising risk with increasing dose of estrogen and with increasing duration of use (55). It has been estimated that a woman's risk of developing endometrial cancer increases ~120% for each 5 years of ERT use (56). Since the 1980s, progestins were added to the ERT, either in a sequential fashion (between 5 and 15 days/month) or CEPRT, to avoid an increase in endometrial cancer risk. Users of SEPRT regimens containing progesterone for <10 days are at increased risk of developing endometrial cancer, but at lower risk when compared with users of ERT, the reduction being proportional to the reduction in the number of days of unopposed estrogen (56). SEPRT regimens including progestin use for ≥ 10 days (usually 14–16) generally are not related to an increase in endometrial cancer risk (56, 57), and use of CEPRT, with continuous presence of progestins, has been associated either with a reduced risk of endometrial cancer or with no risk changes (56–58).

Additional support for the role of unopposed estrogens in endometrial cancer comes from studies on the association of endogenous estrogens and SHBG levels with risk of endometrial cancer. Several case-control studies, but not all (59–67), have shown increased total (18–20, 68–76) and bioavailable (18, 73, 75) estrogens and decreased plasma levels of SHBG (18, 71), in postmenopausal women who developed endometrial cancer compared with cancer-free control subjects. Similar relationships were found recently in one prospective cohort study (77), and in a second study combining a total of 124 cases and 236 controls from three prospective cohorts in New York, Northern Sweden, and Milan. In the latter study, there was an ~6-fold increase in endometrial cancer risk for postmenopausal women in the top quintile of bioavailable E_2 (unbound to SHBG), compared with those of the bottom quintile.⁴

In premenopausal women, one large case-control study showed decreased total and bioavailable E_2 in endometrial cancer patients, although they also had lower levels of SHBG and higher levels of E_1 (18). On first consideration, the decrease in E_2 levels among premenopausal women with endometrial cancer might seem to be at variance with the unopposed estrogen hypothesis. However, it has been argued that in premenopausal women low progesterone, rather than increased estrogen, is the predominant determinant of endometrial cancer risk (36). Proponents of this theory suggest that endometrial cancer risk is related to plasma estrogens only when estrogen concentrations are comparatively low (*i.e.*, within the postmenopausal range of 5–20 pg/ml), and that neither endometrial mitotic activity nor cancer risk increase additionally at E_2 levels above a limit of 50 pg/ml (36). This upper limit was derived from observations that the maximal endometrial mitotic rate is reached in the early follicular phase of the menstrual cycle,

when plasma E_2 concentrations are ~50 pg/ml, without any additional increase in mitotic rate when E_2 levels rise during the late follicular and ovulatory phases. The limit was also approximately consistent with the estimated increase in endometrial cancer risk with estrogen exposures from ERT or with obesity-related increases in plasma E_2 levels in postmenopausal women. The importance of low progesterone is also supported by observations that obesity, a major risk factor for endometrial cancer in both pre- and postmenopausal women, does not increase total or bioavailable estrogens in premenopausal women, but in some women can cause chronic anovulation and strongly reduce progesterone synthesis (see also section 2). The increase in endometrial cancer risk associated with premenopausal use of certain types of SOC does not need to be related to increased estrogenic action at the level of the endometrium but may also be because of the suppression of ovulation and, hence, endogenous progesterone production.

Thus far, no studies have been conducted to examine directly endometrial cancer risk in relation to measurements of endogenous progesterone, and such studies would indeed be quite difficult to design and conduct because of the wide variation in progesterone levels during the menstrual cycle.

Plasma Androgens and Ovarian Hyperandrogenism. Several case-control studies, but not all (60, 62, 64), have shown that endometrial cancer risk is also increased in both pre- and postmenopausal women with elevated plasma levels of $\Delta 4$ -A (18, 19, 72) and T (20, 78). Whereas $\Delta 4$ -A is produced in approximately equal amounts by the adrenal glands and the ovaries, T is produced mainly by the ovaries and from peripheral conversion from other androgens (mostly androstenedione; Ref. 79). Because women at increased risk of endometrial cancer have elevated plasma levels of both $\Delta 4$ -A and T, the increased androgen concentrations in these women appear to be at least in part of ovarian origin. Elevated circulating androgens have also been associated with hyperplasia of the endometrium, which generally precedes and accompanies the occurrence of type I endometrial carcinomas (15, 24, 80, 81).

Additional evidence for an association between endometrial cancer risk and ovarian androgen production comes from observations of increased risk in women with PCOS. PCOS is a complex metabolic syndrome, of which the central characteristics are elevated plasma levels of both T and $\Delta 4$ -A, amenorrhea or oligomenorrhea (signs of anovulatory menstrual cycles), and elevated plasma LH. This constellation of clinical symptoms was first described in the 1930s by Stein and Leventhal, who also noted the association of these symptoms with a polycystic ovarian morphology. Additionally, women with PCOS are insulin resistant and have chronically elevated fasting and nonfasting plasma insulin levels (82). Prevalence estimates of clinical PCOS in premenopausal women vary between 3% and 8%, ranking it among the most common female endocrine disorders (83–86).

There have been frequent case reports of PCOS in women developing endometrial cancer, especially in young patients below the age of 40 (87). Furthermore, several case-control (88–90) and cohort (91, 92) studies have shown an increased risk of endometrial cancer among women who have PCOS, or among infertile women who were clinically characterized by normal plasma estrogen levels but a deficiency of progesterone (which is characteristic of women with PCOS). Relative risk estimates varied from 3.1 to 9.4 (88, 89, 91–93), with an average of ~5.0. Unfortunately, these epidemiological studies did not always distinguish between endometrial cancer occurring before or after menopause. Finally, a number of other

⁴ A. Zeleniuch-Jacquotte *et al.*, Circulating levels of sex steroid hormones risk of endometrial cancer in postmenopausal women, manuscript in preparation.

endocrine similarities between endometrial cancer patients and women with PCOS also suggest that excessive ovarian androgen production may indeed be central to the development of endometrial cancer. First, experiments *in vitro* with ovarian stromal tissue obtained from both endometrial cancer patients (94) and PCOS patients (95, 96) show increased responsiveness of androgen production to insulin stimulation, as compared with the stroma from normoandrogenic control subjects. Second, endometrial cancer patients have increased ovarian vein concentrations of T and Δ 4-A (78, 97), as well as increased 6-h integrated plasma levels of LH (98), the key hormone stimulating ovarian androgen synthesis, which is generally elevated in women with PCOS. Third, increased risk of endometrial cancer has been reported in women with irregular menstrual cycles, an indication of chronic anovulation, which is frequently related to ovarian hyperandrogenism (99, 100).

Although endometrial tissue contains androgen receptors (101, 102), androgens do not appear to have any direct stimulatory effect on endometrial cell proliferation; if anything, the results from *in vitro* studies suggest a reduction in proliferation rates (103–106). The association of plasma androgen levels with endometrial cancer risk is thus more likely to be explained by an increase in estrogens, unopposed by progesterone. In postmenopausal women, plasma androgen levels, especially Δ 4-A, are a key determinant of the amount of estrogens formed in the endometrium and adipose tissue. In premenopausal women, intraovarian androgen excess contributes to follicular atresia, and can lead to chronic anovulation and reduced levels of progesterone (see also section 2).

Insulin. Epidemiological studies have consistently shown an increased risk of endometrial cancer in both pre- and postmenopausal women with noninsulin-dependent diabetes (107–111), a disease that is preceded by many years of increasing insulin resistance, elevated fasting and nonfasting plasma insulin, and which generally remains associated with hyperinsulinemia for many years even after diagnosis. Furthermore, the results from two studies in postmenopausal women suggest an increased risk with hyperinsulinemia even in nondiabetic subjects: one large case-control study showed endometrial cancer risk to be associated with serum levels of C-peptide, a marker of pancreatic insulin secretion (21), and a small study of 32 cancer patients and 18 controls showed cases to have higher fasting plasma glucose and insulin levels (112). A pooled, nested case-control study in cohorts in New York, Northern Sweden, and Milan (combining a total of 170 cases and 323 controls) showed >4-fold increase in endometrial cancer risk for women in the highest *versus* the lowest quintile of plasma C-peptide.⁵ Finally, one small study of 23 endometrial cancer patients and 27 controls showed cases to have decreased plasma levels of IGFBP-1 (113), an IGFBP known to be inversely related to levels of insulin (see also section 2).

A number of mechanisms may link elevated insulin to endometrial cancer development. First, there is evidence that insulin can act as a growth factor, with effects similar to those of IGF-I, although probably weaker. Tumor tissues, including endometrial tumors, generally have increased levels of IGF-I receptors (114–116), and increased insulin receptor content has also been reported (117). Second, it is likely that elevated

insulin increases IGF-I activity in endometrial tissue by suppressing gene expression of endometrial IGFBP-1 (113, 118). Experiments *in vitro* have indeed shown that insulin is a key regulator of IGFBP-1 gene expression and production especially in the liver (119–121), and that it may also reduce IGFBP-1 synthesis in other tissue types, including endometrium (118, 121). Third, insulin provides a key stimulus to ovarian (and possibly also adrenal) androgen synthesis, especially among women with a genetic susceptibility toward development of PCOS (see section 2), and hence may directly contribute to estrogen excess and/or progesterone deficiency. Finally, insulin is a key regulator of the hepatic synthesis and plasma levels of SHBG, down-regulating SHBG levels, and is thus a direct determinant of bioavailable E_2 unbound to SHBG (122–127).

Excess Weight and Endogenous Hormone Metabolism

In section 1, the relationships of endometrial cancer risk with various aspects of endogenous hormone metabolism were reviewed, and low plasma SHBG, elevated plasma androgens (Δ 4-A and T), and elevated total and bioavailable estrogens and insulin were described as major risk factors. Ovarian hyperandrogenism (PCOS), generally associated with chronic anovulation and progesterone deficiency, was also identified as a risk factor. In the present section, we review the relationships of excess weight, another well-documented risk factor for endometrial cancer, with these various alterations of endogenous hormone metabolism.

Insulin, IGF-I, and IGF-binding Proteins. Excess weight is generally associated with insulin resistance, a state of reduced responsiveness of tissues, especially skeletal muscle, liver, and adipose tissue, to the physiological actions of insulin (128, 129). In insulin-resistant states, plasma insulin levels are elevated permanently, even during fasting (130). Insulin resistance induced by excess weight generally develops as a result of increased plasma concentrations of free fatty acids that are continuously released from adipose tissue. The rise in free fatty acid concentrations causes an increase in the hepatic and muscular uptake and oxidation of fatty acids, and this in turn leads to metabolic adaptations that limit the capacity of these tissues to absorb and use glucose for energy metabolism (131–133). These adaptations include a reduction of insulin receptor levels, as well as postreceptor defects in insulin signaling (134–136). Insulin resistance is most strongly related to increases in intra-abdominal body fat stores (“central obesity”; Ref. 137–140) that release free fatty acids into the circulation more rapidly than other adipose tissue compartments (138, 141–144).

In obese subjects, weight loss generally improves insulin sensitivity and normalizes plasma insulin concentrations (145–149). Physical activity generally also improves insulin sensitivity, both in the short and long term (150–161). Whereas long-term effects may be partly because of weight loss, short-term effects must be because of rapid mechanisms that are relatively independent of changes in body weight and composition (157, 162). Consistent with this, cross-sectional studies have indeed shown inverse associations between insulin sensitivity and physical activity levels to be independent of BMI (150–152, 162, 163).

Insulin resistance and chronically elevated plasma insulin levels, in turn, have various effects on the IGF-I/IGFBP system. The most salient of these are decreases in the hepatic production and plasma levels of IGFBP-1 and IGFBP-2 (119–121, 164, 165), and a rise in plasma levels of free IGF-I, a small fraction of IGF-I that is unbound to any IGFBP and that can

⁵ A. Lukanova, P. Toniolo, E. Lundin, A. Micheli, A. Akhmedkhanov, S. Rinaldi, P. Muti, P. Lenner, K. L. Koenig, C. Biessy, V. Krogh, E. Riboli, R. E., Shore, F. Berrino, G. Hallmans, A. Zeleniuch-Jacquotte, and R. Kaaks. Circulating levels of C-peptide, insulin-like growth factor (IGF)-I, IGF binding proteins 1, 2 and 3 and risk of endometrial cancer, submitted for publication.

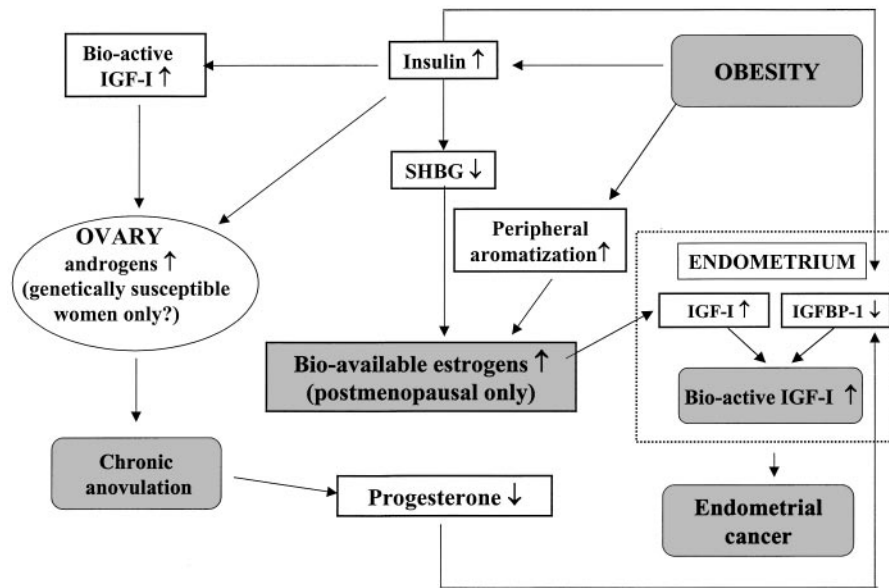


Fig. 1. Endogenous hormones and endometrial cancer development.

freely diffuse from the circulation toward target tissues (Fig. 1; Refs. 166, 167). Plasma-free IGF-I correlates directly with BMI and levels of insulin, and inversely with levels of IGFBP-1 and IGFBP-2 (22). In overweight and obese subjects, weight loss and improvement of insulin sensitivity have been shown to increase levels of IGFBP-1 and IGFBP-2, and to reduce plasma-free IGF-I (10, 164, 168).

Total and Bioavailable Sex Steroids: Normoandrogenic Women. Excess weight and chronic hyperinsulinemia have been associated with changes in total and bioavailable plasma sex steroid levels in both pre- and postmenopausal women. These changes in sex steroid levels can be explained by a number of mechanisms (Fig. 1). First, weight-related increases in insulin and bioactive IGF-I concentrations inhibit the hepatic synthesis of SHBG (124, 169–171). This is generally reflected by inverse associations of BMI and plasma insulin with SHBG, in both pre- and postmenopausal women (126, 172–180). Second, *in vitro* studies have shown that insulin and IGF-I can both enhance the synthesis of androgens by the gonads and adrenal glands (181–183). Third, excess weight results in increased estrogen concentrations from peripheral conversion of androgens (mainly A) to estrogens (mainly E_1) in adipose tissue by aromatase enzyme (184–186).

These various mechanisms have at least three consequences that are identical in pre- and postmenopausal women, namely a decrease in plasma SHBG levels, a rise in E_1 , and a rise in bioavailable T unbound to SHBG. However, the final consequences of excess weight on absolute plasma levels of $\Delta 4$ -A, T, and E_2 , as well as on bioavailable E_2 , are dependent on menopausal status, and may also depend on the presence of additional (most likely genetic) factors that may predispose women to the development of PCOS (Table 1).

After menopause, when ovarian production of estrogens stops, peripheral conversions of $\Delta 4$ -A to E_1 , and then of E_1 into E_2 , both in adipose tissue, become the primary source of endogenous E_2 (184, 187). Thus, in postmenopausal women, the degree of weight excess (BMI) is linearly related to plasma levels of both E_1 and E_2 , as well as to levels of bioavailable E_2

Table 1 Effects of obesity and chronic hyperinsulinemia on plasma sex steroid levels, in pre- and postmenopausal women

	Premenopausal		Postmenopausal
	Normoandrogenic	Hyperandrogenic (PCOS)	
SHBG	↓	↓	↓
E_1	↑	↑	↑
E_2 (total)	~	~	↑
E_2 unbound to SHBG	~	~	↑
$\Delta 4$ -A	~	↑	~ ^a
T (total)	~	↑	~ ^a
T unbound to SHBG	↑	↑↑	↑

^a Observed relationships between obesity/plasma insulin and plasma androgen levels in postmenopausal women are inconsistent across studies, and might depend on genetic factors predisposing to hyperandrogenism.

unbound to SHBG (19, 61, 75, 178, 188–196). Despite the *in vitro* data showing that insulin stimulates androgen production, BMI and plasma insulin concentrations have been found to be only weakly correlated with plasma T levels, but not with levels of $\Delta 4$ -A in postmenopausal women (126, 178, 197, 198).

In normoandrogenic premenopausal women, contrary to postmenopausal women, excess weight and chronic hyperinsulinemia appear to have little effect on levels of either total or bioavailable E_2 (199–202). This might be attributable, first of all, to the relatively small contribution of estrogen production by adipose tissue compared with the ovarian estrogen production. Furthermore, it is possible that in premenopausal women both total and bioavailable estrogen levels are maintained relatively constant through negative feedback of E_2 on the pituitary secretion of follicle-stimulating hormone, the gonadotropin that stimulates ovarian aromatase activity and synthesis of E_2 . Thus, a weight-related decrease in SHBG might be compensated by a reduction in gonadotropin synthesis, and, hence, a reduction in total plasma E_2 . Similar to postmenopausal women, most studies have not shown clear associations of

plasma insulin or BMI with absolute concentrations of $\Delta 4$ -A in normoandrogenic premenopausal women (172, 203–207), although obesity-induced lowering of SHBG concentrations does result in increased levels of total and bioavailable T (125, 127, 174, 203, 206, 208, 209). In both pre- and postmenopausal women, the association of increased weight with plasma T levels seems to be stronger in women with upper body obesity.

In summary, in both pre- and postmenopausal women excess weight decreases plasma SHBG, and increases levels of E_1 and bioavailable T unbound to SHBG. However, only in postmenopausal women does excess weight increase levels of total and bioavailable E_2 , whereas in neither pre- nor postmenopausal women does it normally cause any strong increase in absolute plasma concentrations of $\Delta 4$ -A.

In premenopausal women with ovarian hyperandrogenism (PCOS) the relationships of excess weight and chronic hyperinsulinemia to total and bioavailable sex steroids are different from those in normoandrogenic women. Because of the potential importance of PCOS as a risk factor for endometrial cancer, these relationships are discussed in more detail below.

Total and Bioavailable Sex Steroids: Women with Ovarian Hyperandrogenism. The principal endocrine characteristic of PCOS is a 50–150% increase in circulating levels of T, compared with control subjects with a normal cycle. There is usually also an increase in ovarian production and plasma levels of $\Delta 4$ -A, and in about half of PCOS patients the adrenals also produce increased amounts of $\Delta 4$ -A (210–213). In premenopausal women with PCOS, total and free estrogen levels are usually within the normal range, at a level comparable with that in the normal early and midfollicular phases of the menstrual cycle. However, the high intraovarian androgen levels interfere with follicular development and cause anovulation. As a consequence, estrogen levels often show no preovulatory and midluteal increases and less cyclic variation than in normo-ovulatory women. Because in anovulatory cycles no corpus luteum is formed, there is also a deficit of ovarian progesterone production, and levels of plasma progesterone are low.

Close to half the women with clinical diagnosis of PCOS are severely overweight or obese. When present, obesity generally aggravates the endocrine disturbances of PCOS. Insulin resistance and hyperinsulinemia are present in both lean and obese women with PCOS (207, 214–217) but are more severe in the obese subgroup (207, 215, 217–219). Furthermore, most studies with PCOS patients have shown direct associations of obesity or plasma insulin with levels of total plasma T and $\Delta 4$ -A (204, 220–224), and anovulatory cycles are also more frequent in the obese and more insulin-resistant PCOS patients, probably because of more severe ovarian hyperandrogenism (225–227). As in normoandrogenic premenopausal women, BMI and plasma insulin both correlate inversely with SHBG and IGFBP-1, and directly with levels of bioavailable T unbound to SHBG; thus, additional characteristics of women with PCOS are reduced levels of SHBG and IGFBP-1.

Synthesis and Discussion

We have reviewed current evidence on the associations among endometrial cancer risk, endogenous hormone metabolism, and obesity. Our review started with a summary of the unopposed estrogen hypothesis, which proposes that endometrial cancer may develop as a consequence of progesterone deficiency and/or a relative excess of bioavailable estrogens. As discussed in section 1, it may be largely through the increase in IGF-I bioactivity within endometrial tissue, resulting from estrogen-induced IGF-I synthesis and IGFBP-1 reductions because of

lack of progesterone, that elevated estrogens with low progesterone promotes the development and growth of endometrial tumors. The evidence reviewed suggests that in premenopausal women the major risk factor is a deficit of progesterone, rather than estrogen excess. In postmenopausal women, by contrast, an increase in plasma estrogen levels, of either endogenous or exogenous origin, is clearly associated with (and most likely a cause of) increased endometrial cancer risk.

Apart from elevated E_2 and low progesterone, elevated plasma concentrations of $\Delta 4$ -A, T, and insulin, and reduced levels of IGFBP-1 and SHBG, were also identified as risk factors for endometrial cancer (Fig. 1). As mentioned in section 1, there is little evidence for a direct tumor-promoting effect of androgens through androgen receptors in endometrial tissue. Furthermore, the association of endometrial cancer risk with plasma T levels and history of PCOS suggests that, at least in premenopausal women, endometrial cancer risk is related mainly to ovarian, rather than adrenal, androgen excess. The most likely explanation for the relationship between androgens and endometrial cancer risk in premenopausal women is ovarian hyperandrogenism, leading to chronic anovulation and progesterone deficiency. In postmenopausal women, elevated plasma androgens may increase risk predominantly by leading to increased peripheral estrogen synthesis.

Chronic hyperinsulinemia is clearly another important risk factor for endometrial cancer among both pre- and postmenopausal women. This may be explained by the action of insulin on at least two levels. First, at the level of the endometrium, insulin may stimulate tumor development, by reducing levels of IGFBP-1, thus increasing IGF-I activity. In addition, insulin may directly enhance tumor formation through endometrial insulin receptors. Second, at the level of the ovaries, chronic hyperinsulinemia appears to be a key factor for the development of ovarian hyperandrogenism, associated with anovulation and progesterone deficiency. Indeed, current theories put chronic hyperinsulinemia central in the pathogenesis of PCOS (82). Women with PCOS generally suffer from chronic hyperinsulinemia, and in women with PCOS plasma insulin correlates strongly with androgens and with occurrence of anovulatory cycles. The improvement of insulin sensitivity, either by the use of insulin-lowering drugs or through weight loss, has been shown to lead to a partial or full normalization of plasma androgen levels, and in a large proportion of PCOS patients to the resumption of normal ovulatory menstrual cycles (171, 228–230).

The PCOS combines most, if not all, of the endocrine risk factors for endometrial cancer: chronic hyperinsulinemia, low IGFBP-1, low SHBG, elevated androgens, and lack of luteal-phase progesterone production. Before menopause, obesity and PCOS appear to have little or no effect on circulating total and bioavailable estrogens, and endometrial cancer risk is not directly related to plasma estrogen levels. However, PCOS results in progesterone deficiency, and this suggests again that in premenopausal women progesterone deficiency is the major risk factor. After the menopause, women with PCOS generally continue having a relative excess of ovarian androgen production (231, 232), and the peripheral conversion of the androgens may then cause a relative estrogen excess.

Interestingly, in pre- and postmenopausal women without the clinical symptoms typical of PCOS no strong relationship of plasma T or $\Delta 4$ -A with excess weight or plasma insulin levels has been shown (19, 126, 172, 178, 197, 203–205, 207). This suggests that excess weight and hyperinsulinemia may cause ovarian androgen excess and chronic anovulation only in interaction with additional factors that increase pituitary LH

secretion, or that increase ovarian sensitivity to the steroidogenic stimuli of LH, insulin, or IGF-I. This observation provides additional indirect evidence that PCOS may indeed be a central risk factor for endometrial cancer, because elevated plasma androgens (both $\Delta 4$ -A and T) and elevated BMI often occur together in women who develop endometrial cancer. However, one of the predictions from this model, namely that, at least for premenopausal women, obesity would be associated with increased endometrial cancer risk only if it leads to elevated ovarian androgen production and chronic anovulation, remains to be verified. This prediction implies a statistical interaction between BMI and plasma androgen levels, or between BMI and reported menstrual cycle (ir)regularity, in relation to endometrial cancer risk. Reported results from previous studies do not allow a verification of this hypothesis, and therefore, this question needs to be examined in future studies.

Epidemiological studies suggest an ~5-fold increase in risk of endometrial cancer among women with PCOS. With an estimated population prevalence of PCOS ~8%, this would translate into an ~24% of endometrial cancer incidence because of PCOS. However, it is quite possible that clinically manifest PCOS represents only a “tip of the iceberg,” in that many women may have subclinical forms of ovarian androgen excess and menstrual irregularity, but have symptoms that are not severe enough for them to seek medical advice. An additional fraction of endometrial cancer might be attributable to clinically milder forms of PCOS that often go undetected. Moreover, it is possible that PCOS is a key risk factor especially for endometrial cancer among young, premenopausal women, which again would imply a much higher attributable fraction for that subgroup. Additional studies should be conducted to examine the relationship of endometrial cancer risk with ovarian hyperandrogenism and related chronic anovulation. Such studies might include echographic measurements of ovarian stromal volume, which is related to androgen excess in women with PCOS (233–235).

PCOS is a risk factor of primary interest because its etiology appears to be strongly related to obesity and chronic hyperinsulinemia, risk factors that in principle are modifiable. Given this central position of PCOS, it is of great importance to understand the etiology of this syndrome, and especially of its genetic susceptibility factors, so that potentially one may extrapolate from this knowledge to endometrial cancer etiology. Two different theories about the pathogenesis of PCOS are the “central” (central nervous system) hypothesis (236), which proposes pituitary hypersecretion of LH as the primary event, and the “ovarian” hypothesis, which proposes that PCOS is because of a hyper-response of ovarian steroidogenic enzymes to steroidogenic stimuli such as LH and insulin (181, 211). The familial clustering of PCOS plus some initial evidence from genetic linkage and association studies clearly indicate the importance of genetic background factors in the development of PCOS (212, 237, 238), and in both theories of pathogenesis of PCOS the hypersecretion of LH and/or ovarian hyperresponsiveness is thought to be most likely genetically determined. Furthermore, in both theories PCOS is postulated to develop because of an interaction between these genetic predisposition factors and chronic hyperinsulinemia (237–239). Possible candidate genes for which specific polymorphisms have been found to be associated with PCOS include genes for CYP11A1 (cholesterol side-chain cleavage enzyme; Refs. 239, 240), CYP17 [17 α -hydroxylase/17,20-lyase (241, 242), follistatin (243, 244), insulin (245), and follicle-stimulating hormone (246, 247)]. Thus far, however, none of these polymorphisms have been established definitively as factors predisposing to

PCOS, and none of them have been established as a possible risk factor for endometrial cancer.

Although PCOS seems to be very central in the natural history of endometrial cancer, some proportion of endometrial cancer might also develop in women without a history of PCOS. Before the menopause, other states of chronic anovulation or luteal-phase progesterone deficiency might also be risk factors, although such states probably have a lower population prevalence than PCOS and may not be as clearly linked to excess body weight as PCOS. After menopause, when the ovarian production of progesterone has ceased altogether, endometrial cancer risk might be increased by obesity-related increases in total and bioavailable estrogens, as well as reductions in IGFBP-1, and this might be the case even in the absence of any noticeable increase in plasma androgen levels or of ovarian androgen excess, specifically. Isolated adrenal androgen excess that is unrelated to PCOS might also increase risk especially in postmenopausal women, as it may lead to more elevated estrogen levels. Additional epidemiological studies are needed to establish which proportion of PCOS may be attributable either to a history of ovarian androgen excess combined with chronic anovulation, or to other, unrelated metabolic risk factors.

The high proportion of endometrial cancer incidence attributable to excess weight, and some evidence for an inverse association of endometrial cancer risk with physical activity, indicate the strong potential of weight control and regular physical activity for the prevention of this form of cancer (10). In obese women, weight loss has generally been shown to decrease plasma insulin, and to increase levels of IGFBP-1 and SHBG (10). In obese women with PCOS, weight loss has been shown to normalize plasma androgen levels and lead to the resumption of normal ovulatory cycle (171). Although data on the long-term effects of regular physical activity on endogenous sex hormone metabolism are limited, there is little doubt that regular physical activity will generally help prevent or reduce obesity and insulin resistance (10), and thus contribute to maintaining a plasma sex steroid profile associated with a low risk of endometrial cancer.

In conclusion, evidence suggests that nutrition and lifestyle factors favoring the development of obesity may increase endometrial cancer risk via effects on endogenous hormone and growth factor levels. A central effect in both pre- and postmenopausal women is chronic hyperinsulinemia, and an excess ovarian production of androgens. In premenopausal women, this profile may increase endometrial cancer risk by inducing chronic anovulation and progesterone deficiency. In postmenopausal women, this profile may increase endometrial cancer risk by increasing bioavailable estrogens. Additional epidemiological studies should address the aforementioned questions of possible interactions between excess weight and menstrual cycle irregularity and/or plasma androgen levels in relation to endometrial cancer risk. Future studies are also needed to identify common genetic predisposition factors that, in interaction with lifestyle factors and with obesity, contribute to the development of PCOS, and to examine whether these same polymorphisms and interactions predispose to endometrial cancer development. Finally, studies are needed to estimate the proportion of endometrial cancer incidence, among pre- and postmenopausal women separately, that may be attributed to either ovarian hyperandrogenism or to other mechanisms.

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