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Hormonal interactions in endometrial cancer

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Abstract

Endometrial cancer (EC) is the most frequent malignant tumor of the female genital tract. Increasing evidence suggests that at least two different types of EC exist. Type I is associated with an endocrine milieu of estrogen predominance. These tumors are of endometrioid histology and develop from endometrial hyperplasia. They have a good prognosis and are sensitive to endocrine manipulation. Type II EC is not associated with a history of unopposed estrogens and develops from the atrophic endometrium of elderly women. They are of serous histology, have a poor prognosis, and do not react to endocrine manipulation. Both types of EC probably differ markedly with regard to the molecular mechanisms of malignant transformation. This article reviews reproductive and lifestyle factors modifying the risk of developing type I EC, including the use of hormonal contraceptives, hormone replacement therapy and tamoxifen. The roles of established and novel therapies for precancerous lesions and for invasive EC in the adjuvant and palliative settings are discussed.

Introduction

Endometrial cancer (EC) is the most common malignancy of the female genital tract. In Western industrialized countries, annual incidence rates of between 10 per 100 000 women (UK, Spain, France) and 25 per 100 000 women (USA, Canada) are observed (Parazzini *et al.* 1991). In the USA, for 1998, an estimated 36 000 new cases and 6300 deaths will be attributed to endometrial cancer (Podratz *et al.* 1998). In Sweden, carcinoma of the endometrium is the third most frequent cause of cancer death in women, next after breast and colon cancer. In the USA, EC is ranked fourth after breast, lung and colon cancer (Li *et al.* 1999). The lifetime risk for a woman to develop EC is 1 in 38 in the USA. The incidence increases steadily with age and peaks between the ages of 70 and 74 years (112/100 000 women) before slightly falling (Ball & Elkadry 1998), making the disease a significant factor in women's health in an aging population. EC is relatively uncommon in the younger age group, and women below the age of 45 represent only 2–14% of all cases (Vinker *et al.* 1999). About 20–25% of women with EC, however, are premenopausal (Creasman 1997). The prognosis for EC is excellent in the early stages, when the tumor is confined to the endometrium (Stage Ia: 5-year survival=91%) or to the inner 50% of the myometrium (Stage Ib: 5-year survival=88%) (Creasman *et al.* 1998). Five-year survival decreases to 81% when the tumor infiltrates the outer half of the myometrium (Stage Ic), to 77–67% when the cervix is engaged (Stage II) and to 60–52% when there are tumor manifestations outside the uterus (Stage III) (Creasman *et al.* 1998). In Stage IVb (distant metastases), only 5% of affected women survive 5 years (Creasman *et al.* 1998). Fortunately, most patients with EC present with early stage disease, because of typical early symptoms (bleeding disorders or vaginal discharge), resulting in an overall 5-year survival rate for EC of 73% (Creasman *et al.* 1998).

The mainstay of therapy for EC is the surgical removal of tumor manifestations. In the majority of cases this is achieved by total abdominal hysterectomy and bilateral salpingoophorectomy (Ball & Elkadry 1998). The role of diagnostic and therapeutic lymphadenectomy is currently the subject of debate (Ball & Elkadry 1998). The role of adjuvant postoperative radiation in the management of operable EC remains unresolved, though it is routinely performed in many centers (Cohen & Rahaman 1995, Ball & Elkadry 1998, Podratz *et al.* 1998). Patients who are not candidates for surgery, because of an advanced tumor stage or underlying medical problems, are often treated with radiotherapy alone (Ball & Elkadry 1998).

For patients with recurrent EC not eligible for surgery or radiotherapy or for those women primarily with advanced disease, a systemic treatment is the only remaining option. Chemotherapy for recurrent or advanced EC induces

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response rates of up to 60% but is of limited benefit as progression-free survival is only in the range of some months (Moore *et al.* 1991, Burke & Gershenson 1996, Homesley 1996, Ball & Elkadry 1998, Quinn 1999). So far, there is also no evidence that adjuvant chemotherapy for the EC patient with a high risk of recurrence has any substantial benefit (Moore *et al.* 1991, Burke & Gershenson 1996, Homesley 1996, Quinn 1999).

Because EC develops from the endometrium, a classical hormone-dependent tissue, endocrine therapies have been the mainstay of systemic treatment for many decades. In addition, adjuvant endocrine therapies for high-risk disease have been commonly used. In this paper, we review the present knowledge on endocrine factors in the etiology of EC, their role in the regulation of proliferation and metastases formation, and the potential value of both established and novel endocrine manipulations for the prevention and treatment of EC.

Etiology

It has been acknowledged for more than 50 years that continuous exposure to estrogens in the absence of sufficient levels of progestogens promotes the development of EC. Typical risk factors are obesity, anovulatory states, early menarche and late menopause, nulliparity and unopposed exogenous estrogens (Table 1). EC in these cases develops via a characteristic sequence of hyperplastic changes of the endometrium with increasing premalignant potential (simple hyperplasia or complex hyperplasia, both types either with or without atypia) (Bokhman 1983, Deligdisch & Cohen 1985, Deligdisch & Holinka 1986, Nyholm *et al.* 1993*a*, Cohen & Rahaman 1995, Sherman 2000). Histologically, these estrogen-related ECs are accompanied by endometrial hyperplasia. They are well-to-intermediately differentiated, are normally diagnosed at an early stage, and have an excellent prognosis. They strongly express estrogen and progestin receptors and have high response rates to progestin treatment of advanced stages (Bokhman 1983, Deligdisch & Cohen 1985, Deligdisch & Holinka 1986, Nyholm *et al.* 1993*a*,*b*, Cohen & Rahaman 1995, Sivridis *et al.* 1998, Sherman 2000) (Table 1). Since the pioneer work of Bokhman (1983) and of Deligdisch and colleagues (Deligdisch & Cohen 1985, Deligdisch & Holinka 1986), a second type of EC has been identified which is not associated with hyperestrogenic states. It develops from the atrophic endometrium of older women, who do not have the classical risk factors for EC. These patients tend to be slim, are physically fit, and have never used estrogen-replacement therapy. These type II ECs are mostly of a high grade or have high-risk histology (serous-papillary or clear-cell carcinomas). On diagnosis, they are characterized by deep myometrial invasion and early lymph node or distant metastases. Type-II ECs rarely express functional estrogen and/or progestin receptors and their response rates to endocrine therapies tend to be low. Their prognosis is poor. Type-II ECs are estimated to represent 20% up to more than 50% of all endometrial cancers (Bokhman 1983, Deligdisch & Cohen 1985, Deligdisch & Holinka 1986, Nyholm *et al.* 1993*a*, Cohen & Rahaman 1995, Sivridis *et al.* 1998, Sherman 2000) (Table 1). Recently, a classification into three types of EC (I: endometrioid carcinomas associated

Table 1 Two different types of endometrial cancer (according to Bokhman 1983, Deligdisch & Cohen 1985, Deligdisch & Holinka 1986; Nyholm *et al.* 1993*a*, Cohen & Rahaman 1995, Sivridis *et al.* 1998, Sherman 2000)

Parameters	Type I	Type II
Menstrual history	Anovulatory bleedings	No disorders
Fertility	Reduced; infertility	No disorders
Age at menopause	>50 years	<50 years
Vaginal cytology during postmenopause	Estrogen activity	Atrophic
Age at diagnosis	Perimenopausal	Late postmenopause/senium
Ovarian histology	Stromal hyperplasia, polycystic ovarian disease, estrogen-producing tumors	Fibrosis
Status of tumor-free endometrium	Hyperplasia	Atrophic
Myometrium	Leiomyosis, fibroids	No abnormality
Obesity	Often present	Absent in most cases
Hyperlipidemia	Often present	Absent in most cases
Diabetes mellitus	Often present	Absent in most cases
Duration of symptoms	Mostly long	Mostly short
Grading of the tumor	>80% G1, G2	>60% G3 or ungraded
Histological type	Mostly endometrioid cancers	Often serous papillary, clear cell, squamous carcinomas
Myometrial invasion	Mostly superficial	Mostly deep
Lymphatic invasion	Rare	Common
Expression of progesterone receptor	High	Low
Prognosis	Favorable	Poor

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with hyperplastic endometrium; II: endometrioid carcinomas associated with atrophic endometrium; III: non-endometrioid carcinomas associated with atrophic endometrium) has been suggested (Sivridis *et al.* 1998). The authors, however, point out that this subdivision, though possibly important pathogenically, does not have any therapeutic implications. Non-endometrioid adenocarcinomas and deeply invasive or poorly differentiated endometrioid carcinomas require aggressive treatment, but well-differentiated endometrioid carcinomas arising from an atrophic background can be treated in the same manner as those of a similar grade associated with an endometrial hyperplasia (Sivridis *et al.* 1998).

In a very recent paper, Sherman (2000) also suggests the existence of two major types of EC: (1) the most common type, endometrioid adenocarcinoma, represents over 80% of ECs that develop from endometrial hyperplasia in the setting of excess estrogen exposure and pursues an indolent clinical course; and (2) a minority of ECs, best represented by serous carcinoma, do not seem to be related to estrogenic risk factors or elevated serum hormone levels. These type II tumors seem to develop from atrophic rather than hyperplastic epithelium (Sherman 2000). Apart from these two well-defined types of EC, Sherman also acknowledges a third group, where endometrioid carcinomas are associated with atrophic endometrium (29% of all endometrioid ECs). In addition, mixed endometrioid/serous carcinomas exist, which, in 46% of cases, are associated with endometrial hyperplasia (Carcangiu & Chambers 1992). Finally, 5–8% of pure serous ECs were found to be associated with endometrial hyperplasia (Carcangiu & Chambers 1992, Ambros *et al.* 1995). Although the definition of this third group of ECs is still unsatisfactory from an etiologic point of view, these cancers usually share the high-risk characteristics of non-endometrioid tumors and are to be treated accordingly (Sivridis *et al.* 1998, Sherman 2000). Because of the lack of data on this third group, the present review will focus on the much better-defined 'estrogen-driven' endometrioid ECs and the estrogen-unrelated non-endometrioid ECs, best represented by serous carcinoma.

Etiology of estrogen-associated endometrial cancer (type I)

The association between an endocrine milieu of estrogen predominance, resulting in hyperstimulation of the endometrium, and an increased incidence of EC was first formally reported in 1947 (Gusberg 1947). Later, pathologists defined the cytologic and architectural patterns of endometrial hyperplasia more precisely; this led to a better definition of the premalignant potential of ECs. In a series of 170 patients who received no therapeutic intervention other than diagnostic curettage, Kurman *et al.* (1985) found that 23% of patients with atypical endometrial hyperplasia developed carcinoma compared with only 2% of patients with other types of hyperplasia.

Hormone-replacement therapy

The association between an estrogen-dominant endocrine milieu and type I EC is most comprehensible for the example of hormone-replacement therapy in peri- and postmenopausal women. A meta-analysis of 30 evaluable studies defined a relative risk (RR) for EC of 2.3 (95% confidence interval (CI): 2.1–2.5) for women on exclusive estrogen-replacement therapy (ERT) compared with women receiving no hormone substitution (Grady *et al.* 1995). ERT given for 10 and more years led to an increase of RR for EC to 9.5. The increase in the RR for EC remains elevated even after discontinuation of ERT for 5 and more years (Grady *et al.* 1995).

The combination of progestins with ERT markedly reduced the RR for EC to 0.8 (95% CI: 0.6–1.2) (Grady *et al.* 1995). When only cohort studies were analyzed, combined estrogen/progestin replacement therapy even reduced the RR for EC to 0.4 (95% CI: 0.2–0.6), suggesting a protective effect compared with women receiving no hormone replacement (Grady *et al.* 1995). In a recent case-control study, Pike *et al.* (1997) found that the RR for EC was 2.17 (95% CI: 1.91–2.47) per 5 years of ERT use. For women who received sequential estrogen–progestin replacement therapy, with the progestin being given for less than 10 days (effectively 7 days) per month, the RR was only slightly reduced, to 1.87 (95% CI: 1.32–2.65) per 5 years of use. However, when progestin was given for 10 or more days (effectively 10 days), there was essentially no increased risk (RR=1.07 per 5 years of use; 95% CI: 0.82–1.41). Continuous combined replacement therapy was also associated with essentially no increased risk (RR=1.07 per 5 years of use; 95% CI: 0.8–1.43). The authors concluded that the progestin in sequential estrogen–progestin replacement therapy needs to be given for at least 10 days to block any increased risk of EC effectively. Continuous combined estrogen–progestin therapy is similarly effective. Neither regimen reduced a woman's underlying risk of EC (Pike *et al.* 1997).

Weiderpass *et al.* (1999*a*), when conducting a nationwide population-based, case-control study in Sweden found that 5 or more years of exclusive ERT was associated with a marked duration- and dose-dependent increase in the RR of EC. Five and more years of treatment had an RR of 6.2 for estradiol (95% CI: 3.1–12.6) and an RR of 6.6 for conjugated estrogens (95% CI: 3.6–12.0). Following combined estrogen–progestin use, the association was considerably weaker than that for estrogen alone; the RR was 1.6 (95% CI: 1.1–2.4) after 5 or more years of use. This increase in risk was confined to women with cyclic use of progestins, i.e. use for fewer than 16 days per cycle (most commonly 10 days per cycle): RR=2.9 (95% CI: 1.8–4.6 for

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5 or more years of use). In contrast, continuous progestin use along with estrogens was associated with a reduced risk (RR=0.2; 95% CI: 0.1–0.8 for 5 or more years of use) (Weiderpass *et al.* 1999*a*).

Even low doses of unopposed estrogens or the oral use of a low-potency estrogen (estriol) increase the risk of EC. Cushing *et al.* (1998) found an RR of 5.4 (95% CI: 2.3–13) for EC in women who had taken 0.3 mg unopposed conjugated estrogens per day. The risk was particularly high in women whose use of this dose was both current and of more than 8 years' duration (RR=9.2; 95% CI: 2.9–29) (Cushing *et al.* 1998). Weiderpass *et al.* (1999*b*) found that the oral use of estriol (1–2 mg), which is assumed to have few, if any, adverse effects on the endometrium, increased the RR of EC and endometrial atypical hyperplasia. After at least 5 years of oral estriol replacement, the RRs were 3.0 (95% CI: 2.0–4.0) for invasive EC and 8.3 (95% CI: 4.0–17.4) for atypical endometrial hyperplasia. Only weak associations were observed between vaginal application of estriol formulations and the RR of endometrial hyperplasia (Weiderpass *et al.* 1999*b*). Women receiving ERT who develop endometrial cancer have traditionally been thought to develop good-prognosis tumors of low grade and early stage. However, a recent case-control study found that, women who took unopposed estrogens for 3 or more years had a fivefold increase in the risk of myometrial invasion and almost a threefold risk of high-grade tumors, risks which were negated by the use of cyclical or continuous progestins (Shapiro *et al.* 1998).

Although there are a few differences between the above observational studies, they are only marginal. These studies unequivocally find a significant time-dependent increase of the RR for EC induced by hormone-replacement therapy with unopposed estrogens during peri- and postmenopause. Combination with progestins significantly reduces this excess risk for EC caused by estrogen replacement. The protective effect of progestins seems to increase with their duration of use per month. The data suggest that progestins should be used for at least 10 days per replacement cycle, or even as a continuous combination with estrogens, to achieve a maximal reduction in the estrogen-induced excess risk for EC.

Disorders of the menstrual cycle

An endocrine milieu similar to that associated with unopposed ERT is found in women with anovulatory cycles or corpus luteum insufficiency (CLI), states which are characterized by a complete or relative deficiency of endogenous progesterone. CLI and anovulatory cycles occur not only in infertile women of reproductive age but are characteristic of the premenopausal period. Thus, a late menopause or a premenopause complicated by intensive bleeding disorders due to CLI or anovulatory cycles are typical risk factors for EC (Barakat *et al.* 1997).

Estrogen-producing tumors and polycystic ovary syndrome

Estrogen-producing tumors and polycystic ovary syndrome (PCOS) also induce an endocrine milieu of estrogen predominance. PCOS is characterized by the absence of ovulations and thus endogenous progesterone production and an increased secretion of ovarian androgens which are peripherally converted to estrogens (Barakat *et al.* 1997). Estrogen-producing tumors and PCOS carry a high risk for EC in young women (Cohen & Rahaman 1995, Barakat *et al.* 1997).

Obesity/metabolic syndrome

A comparable pathophysiologic mechanism explains the significant association between obesity and risk for EC. Adrenal androgens are converted to estrogens by aromatases in the adipose tissue (Gusberg 1994). Hyperinsulinemia, which is common in obese women, additionally stimulates androgen synthesis by postmenopausal ovaries; hypercorticism contributes to increased adrenal androgen production (Nagamani *et al.* 1988, 1992*a*, Goodman *et al.* 1997, Troisi *et al.* 1997). In addition, direct growth-promoting activity of insulin in EC cells has been demonstrated (Nagamani & Stuart 1998).

Postmenopausal women with EC have significantly elevated levels of bioactive luteinizing hormone, a factor probably contributing to increased ovarian androgen production (Nagamani *et al.* 1992*b*). The aromatization of adrenal and ovarian androgens leads to significantly elevated plasma levels of estrone and estradiol (Nyholm *et al.* 1993*b*). As in breast cancer cells, aromatase activity in endometrial cancer cells or in the desmoplastic stroma surrounding the tumor cells might be of additional importance (Bulun *et al.* 1994, Watanabe *et al.* 1995).

Sherman *et al.* (1997), when performing a case-control study of 328 patients with endometrioid EC and 26 with serous EC, found that both the estrogen and the androgen serum levels were elevated in women with endometrioid EC, compared with controls.

Diet and lifestyle

Women with diets high in energy and fat and low in complex carbohydrates including vegetables, fruits, cereals and grains were at increased risk of EC, a phenomenon which was more pronounced in obese women (Goodman *et al.* 1997). The association with fruit and vegetable intake is considered to be less clear by other authors, who found physical activity, number of pregnancies, and weight in young and middle age

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to be the most important lifestyle factors modifying EC risk (Terry *et al.* 1999).

Cigarette-smoking has been found to reduce the risk of EC significantly, according to a number of observational studies (reviewed by Parazzini *et al.* 1995). This phenomenon is explained by the induction of earlier menopause and by the induction of liver enzymes inactivating circulating estrogens. Although this 'protective' effect of cigarette-smoking is more than counteracted by the other carcinogenic effects of this habit, it supports the concept of the impact of estrogen dominance in the pathogenesis of EC (Parazzini *et al.* 1995).

Hormonal contraception

The use of oral contraceptives (OCs) significantly reduces the risk of EC. This protective effect increases with duration of use, is most prominent with continuously combined preparations, and persists for many years after discontinuation of OC use (La Vecchia *et al.* 1996, Brinton & Hoover 1997). A comparable protective effect has been attributed to the contraceptive use of depot medroxy-progesterone acetate (Lumbiganon 1994).

Unopposed estrogens: mitogens or mutagens?

The common denominator for the above phenomena is that a shift in the estrogen–progestin balance towards a predominance of estrogens favors the development of EC, whereas a relative or absolute increase in progestin exposure has a protective effect. (Fig. 1). Morphologically, an estrogen predominance induces the typical sequence of endometrial hyperplasia, finally resulting in the development of EC (Gusberg 1994). Estrogen stimulation of the endometrium increases mitogenic activity, whereas this activity is reduced by progestins (via different anti-estrogenic mechanisms, including a reduction in estrogen receptors and an increase in metabolic inactivation of estrogens). In addition, the mitotic activity of the endometrium is reduced by progestins through the induction of cellular differentiation, thus counteracting the development of hyperplasia (Lupulescu 1993, Gusberg 1994, Berchuk & Boyd 1995, Cohen & Rahaman 1995, Kumar *et al.* 1998). There is no evidence that physiological levels of estrogens or concentrations achieved with their therapeutic use are directly carcinogenic for human cells (Lupulescu 1993, Berchuk & Boyd 1995). Rather, it is assumed that the increased mitotic activity of the endometrium caused by estrogen predominance increases the probability of the accumulation of random mutations (activation of oncogenes, inactivation of tumor-suppressor genes), finally leading to malignant transformation. Thus, estrogens probably act as tumor promoters but not as carcinogens in EC. Their action is believed to be mitogenic but not mutagenic (Lupulescu 1993, Gusberg 1994, Berchuk & Boyd 1995).

Recently, it has been suggested that estradiol is additionally a weak carcinogen and mutagen capable of inducing genetic lesions with low frequency. Tumors may be initiated by the metabolic conversion of estradiol to 4-hydroxyestradiol and by further activation of this catechol to reactive semiquinone/quinone intermediates that cause the DNA damage. Tumors may develop by means of further hormone-receptor-mediated proliferation of such damaged cells (Liehr 2000). Liehr, however, stresses the point that the mutagenic activity of estradiol is weak, as high mutagenic and carcinogenic activity of estradiol would not have permitted the existence of many higher life-forms, including humans (Liehr 2000).

Etiology of non-estrogen-associated endometrial cancer (type II)

Histopathologic studies suggest that the majority of serous carcinomas develop from a distinctive lesion termed endometrial intraepithelial carcinoma, which appears to represent malignant transformation of atrophic surface endometrium (Ambros *et al.* 1995, Sherman 2000). In uteri containing serous carcinoma, the uninvolved endometrium is usually atrophic. It has been shown that when endometrial hyperplasia is identified in a uterus containing a carcinoma that is partly or exclusively serous, the hyperplasia and the carcinoma are usually topographically unrelated and appear distinct (Sherman 2000). In the case-control study by Sherman *et al.* (1997), obesity and exogenous hormone use were not related to risk for serous carcinoma. Serum estrogen and androgen levels for patients with serous carcinoma were similar to those in the controls. In contrast, levels of sex-hormone binding globulin, a circulating protein that reduces bioavailable estrogen, were higher among serous carcinoma patients than in controls or endometrioid carcinoma patients (Sherman *et al.* 1997). The only risk factors for non-estrogen-related EC that can be assumed today are age (Deligdisch & Cohen 1985, Cohen & Rahaman 1995, Sivridis *et al.* 1998, Sherman 2000) and pelvic irradiation (Sivridis *et al.* 1998). With advancing age, the probability of the accumulation of mutations leading to malignant transformation increases (Berchuk & Boyd 1995). Pelvic irradiation might also add to the accumulation of mutations. The declining competence of the immune system with advancing age has been suggested as a further possible reason (Deligdisch & Cohen 1985, Cohen & Rahaman 1995, Deligdisch & Holinka 1986) (see Fig. 2).

Molecular findings regarding the etiology of endometrial cancer

Most molecular studies of EC have consisted of small series reported from single institutions (reviewed by Berchuk &

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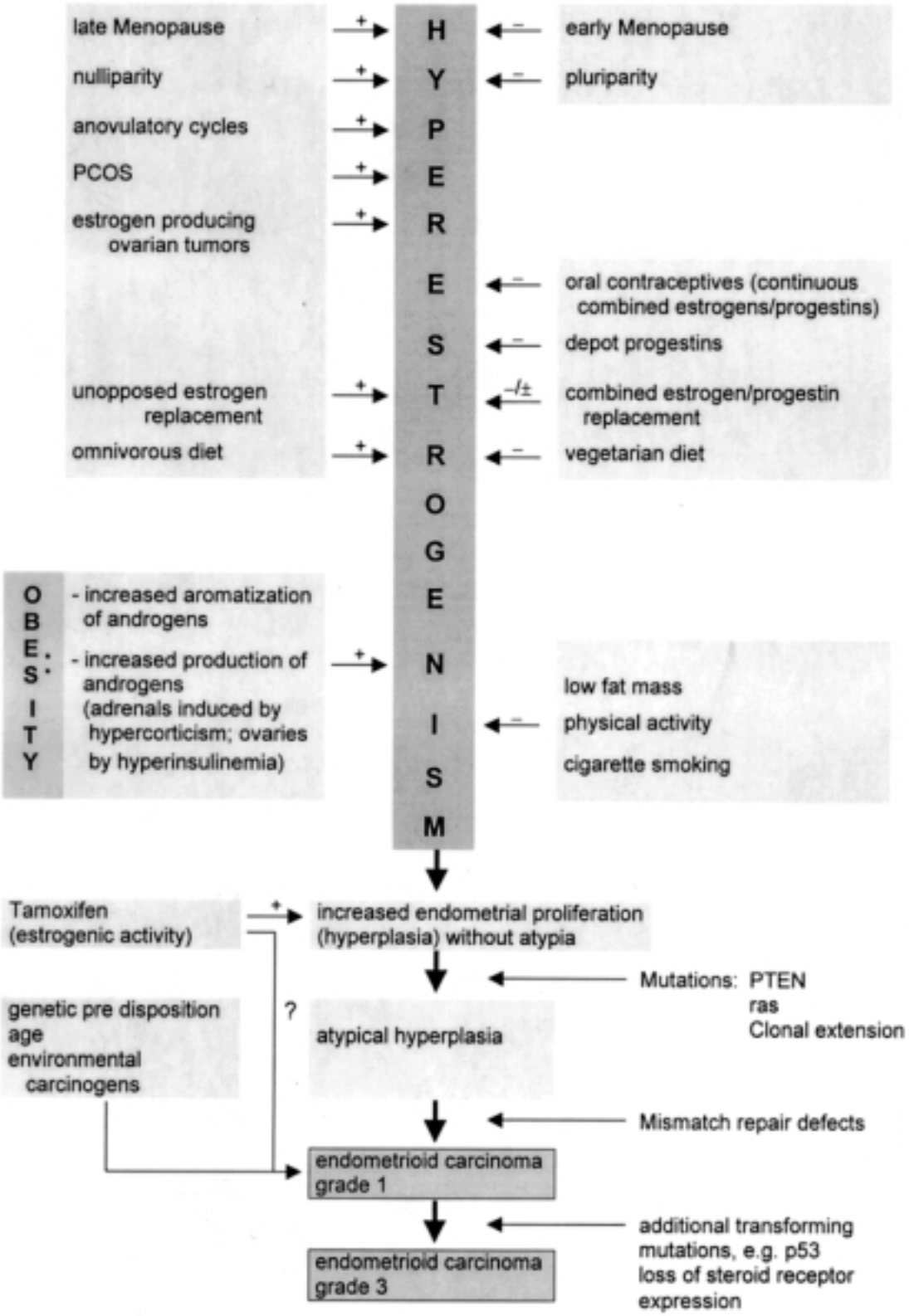

Figure 1 Model of carcinogenesis of endometrial cancer type I (estrogen-related).

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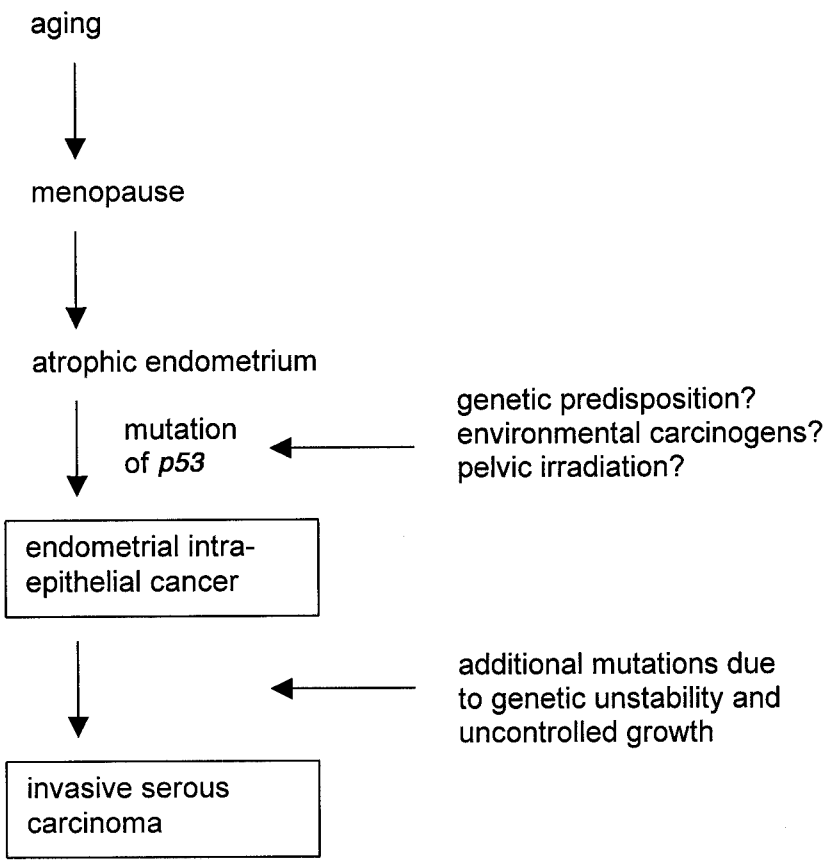

Figure 2 Model of carcinogenesis of endometrial cancer type II (non-estrogen-related) (modified according to the model of Sherman 2000).

Boyd 1995, Jeyarajah *et al.* 1996*a*; Terakawa *et al.* 1996, Niederacher *et al.* 1999) (Table 2). The interpretation of these data was further complicated by the fact that most authors made no clear distinction between type I (estrogen-related) and type II (non-estrogen-related) ECs. Taking into account the very recent literature, as well as the elegant dualistic model of endometrial carcinogenesis proposed by Sherman (2000), the somewhat confusing molecular data might be interpreted as described below.

Endometrioid EC (type I)

In most cases, these cancers evolve from atypical endometrial hyperplasia as a clonal lesion (Mutter *et al.* 1995, 1996, Sherman 2000).

Mismatch repair defects

The microsatellite instability or replication error repair (RER) phenotype has been reported in 9–45% of sporadic endometrioid carcinomas (Mutter *et al.* 1996, Gurin *et al.* 1999, MacDonald *et al.* 2000). Microsatellite instability was detected in atypical hyperplasia associated with carcinoma but not in atypical hyperplasia without associated carcinoma (Mutter *et al.* 1996), suggesting that mismatch repair defects may occur in the transition between the two lesions (Sherman 2000). Somatic mutational inactivation of known mismatch repair genes, however, does not account for the great majority of sporadic ECs with microsatellite instability. A significant fraction of these cases may be causally associated with hypermethylation of the *MLH1* promoter, resulting in a loss of repair function without mutation (epigenetic effect) (Gurin *et al.* 1999).

ras mutations

ras mutations have been reported in 10–46% of endometrioid ECs (Berchuk & Boyd 1995, Jeyarajah *et al.* 1996*a*, Terakawa *et al.* 1996, Niederacher *et al.* 1999). *ras* mutations have been detected in 10% of simple, 14% of complex, and

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Table 2 Molecular events in sporadic endometrial cancer (according to Gurpide 1991, Jeyarajah *et al*. 1996*a*, Terakawa *et al*. 1996, Niederacher *et al*. 1998, Reynolds *et al*. 1998, Niederacher *et al*. 1999, Quinn 1999, Sherman 2000).

Overexpression/amplification of growth factors and/or their receptors (EGF, IGF-I, IGF-II, TGF-α, PDGF, M-CSF, C fms, HER-2/neu-protein)*
Mutation of K-*ras* (proto-oncogene, signal transduction)
Amplification of other oncogenes (c-*myc*, *int*-2)
Mutations/loss of heterozygosity of tumor suppressor genes (*TP 53*, *BRCA1, TCRD, DCC, PTEN*)
Mutation of DNA-repair genes (*MSH-2, MLH-1*)
Loss of expression of estrogen/progesterone receptors, mutations in these receptors, changes in the relationships of isoforms of estrogen and/or progesterone receptors
Overexpression of genes relevant to metastasis formation (cathepsin D, urokinase-type-plasminogen activator, CD 44 and others)

*EGF, epidermal growth factor; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; TGF-α, transforming growth factor-α, PDGF, platelet-derived growth factor; M-CSF, macrophage-colony stimulating factor.

22% of atypical hyperplasias, suggesting that these mutations may be an early event in the development of EC (Berchuck & Boyd 1995, Jeyarajah *et al.* 1996*a*, Sherman 2000). Mutations in the *ras* oncogene enhance estrogen- and tamoxifen-induced transcription activity of estrogen receptor (ER) activation function 1 (Niederacher *et al.* 1999).

PTEN mutations

The tumor suppressor gene *PTEN* (Dahia 2000) is mutated in 40% of endometrioid ECs and in both atypical hyperplasias associated with carcinoma and those that have not progressed to invasive carcinoma (Risinger *et al.* 1997, Maxwell *et al.* 1998, Sherman 2000). Mutations in *PTEN* have been identified in up to 86% of endometrioid carcinomas with microsatellite instability, suggesting a relationship between these two lesions, although the mutations in *PTEN* do not involve microsatellite sequences. In a very recent paper, Mutter *et al.* (2000) found *PTEN* mutations in 83% of endometrioid ECs and 55% of premalignant lesions, whereas no normal endometria showed *PTEN* mutations. Cancers and most precancers exhibited contiguous groups of *PTEN*-negative glands, whereas endometria altered by unopposed estrogens showed isolated *PTEN*-negative glands. These authors pointed out that highly mitotic cells, such as normal estrogen-stimulated proliferative endometrial glands, contain abundant PTEN protein. Suppression of *PTEN* expression in a mitotically active estrogenic environment (unopposed by progestins) may compromise growth control more than loss of PTEN protein in mitotically quiescent cells. Thus, loss of *PTEN* function by mutational or other mechanisms is an early event in endometrial tumorigenesis of the endometrioid type. These authors conclude that individual *PTEN*-negative glands in estrogen-exposed endometria are the earliest recognizable stage of endometrial carcinogenesis, it being followed by proliferation into dense clusters that form discrete premalignant lesions (Mutter *et al.* 2000).

p53 mutations

p53 mutations are rare in endometrioid EC. Most endometrioid carcinomas that harbor *p53* mutations are large high-grade tumors, which suggests that *p53* mutation in endometrioid carcinoma is more closely related to dedifferentiation, as in the case of other tumor systems (Sherman 2000).

Hormone receptors

Estrogen and progesterone receptors are usually found in high concentrations in endometrial hyperplasia and endometrioid carcinomas of low grade and stage. Steroid receptor expression diminishes with increases in stage and grade (Kleine *et al.* 1990, Nyholm *et al.* 1992, Creasman 1997) (Fig. 1).

Non-endometrioid ECs (type II)

These cancers rapidly develop from endometrial intraepithelial carcinoma, which appears to represent malignant transformation of atrophic surface epithelium (Sherman 2000). Microsatellite instability and mutations in *ras* and *PTEN* are not found in serous carcinoma (Sherman 2000). The typical molecular features of this type of EC are mutations in the *p53* tumor suppressor gene and accumulation of *p53* protein, which are found in approximately 90% of both serous ECs and their precursor lesions, endometrial intraepithelial carcinomas (Sherman *et al.* 1995, Moll *et al.* 1996, Tashiro *et al.* 1997, Sherman 2000). Steroid receptors are not expressed in serous carcinoma (Moll *et al.* 1996, Sherman 2000) and endometrial intraepithelial carcinoma, although the atrophic endometrium in which these tumors arise is receptor-positive (Sherman 2000) (Fig. 2).

New findings on hormone receptors

Estrogen and progesterone receptors

At the end of 1995, a second ER (ERβ) with different regulatory functions was cloned. Estradiol may activate transactivation through the classic estrogen receptor (ERα) but inhibit transcription through ERβ (Enmark & Gustafsson

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1998). First reports are now appearing on the expression of ER isoforms in gynecological tumors (Chu *et al.* 2000) including ECs (Saegusa & Okayasu 2000). The latter paper reports that relative amounts of ERα at both mRNA and protein level were significantly greater than those for ERβ in normal and malignant endometrial lesions. ERα mRNA showed a stepwise decrease from normal endometrium or grade (G) 1 to G3 tumor lesions, in line with changes at the protein level. In contrast, ERβ mRNA or protein expression did not alter, suggesting a shift in the ratio of the two ER subtypes during endometrial tumorigenesis. Progesterone receptor (PR) mRNA was significantly correlated with ERα, but not ERβ mRNA status (Saegusa & Okayasu 2000). Similarly, two distinct forms of PR receptors (PR-A and PR-B) exist in the female genital tract and might be differentially regulated in EC. Downregulation of PR-B in poorly differentiated human ECs might be involved in the resistance of these cancers to progestin therapy (Kumar *et al.* 1998).

Exon deletions and variants of human ER mRNA in endometrial hyperplasia and adenocarcinoma have been described recently, suggesting that differing ER proteins are present in EC and may influence estradiol signaling pathways (Horvath *et al.* 2000).

Receptors for gonadotrophin releasing hormone

Recently, a series of papers from different laboratories has demonstrated the expression of gonadotropin-releasing hormone (GnRH) and its mRNA in almost 100% of ECs and the expression of the GnRH receptor and its mRNA in about 80% of ECs (for a review see Emons *et al.* 1997). GnRH-agonists and -antagonists dose-dependently inhibit the proliferation of human EC cell lines that express GnRH receptors, probably through inhibition of mitogenic signal transduction (Emons *et al.* 1997, Gründker & Emons 1999, Gründker *et al.* 2000). In addition, spontaneous and growth-factor-stimulated proliferation of human EC cell lines can be inhibited by agonistic analogs of somatostatin through specific somatostatin receptors (Emons *et al.* 1996).

Hereditary forms of EC

The best-documented form of familial EC occurs as part of the Lynch II syndrome, which describes a subgroup of the hereditary non-polyposis colorectal cancer (HNPCC) syndrome in which colorectal, endometrial, breast and ovarian tumors are inherited in an autosomal dominant fashion. The molecular base for this syndrome are germ-line mutations of DNA-repair genes (*MSH2* or *MLH1*) (Vasen *et al.* 1994, Jeyarajah *et al.* 1996*a*). Women from these families have a lifetime risk of developing EC of 20–30%. Typically, these ECs are diagnosed approximately 15 years earlier than those in the general population (Vasen *et al.* 1994). The Lynch II syndrome accounts for only a small proportion of ECs. It was shown, however, that first-grade female relatives of EC patients have an increased risk for EC (Lynch *et al.* 1994). The relative risk of EC as well as that for other cancers is significantly elevated in family members of breast cancer patients (Assikis & Jordan 1996, Jeyarajah *et al.* 1996a).

Tamoxifen and EC

For about 15 years, it has been known that the anti-estrogen tamoxifen (TAM) is able to stimulate the proliferation of certain EC cell lines (Gusberg 1994, Cohen & Ramahan 1995, Assikis & Jordan 1996, Homesley 1996, Creasman 1997). These findings attracted public concern when data from several large trials on TAM use in adjuvant therapy for early breast cancer suggested an excess risk of EC for women taking TAM as compared with controls (Assikis & Jordan 1996, Creasman 1997). It has also been proposed that TAM-associated ECs tend to be more often of the high-risk type compared with those in the general population (Assikis & Jordan 1996). After years of discussions, in the public and the scientific communities, which were stimulated by contradictory results of clinical trials (Creasman 1997), the Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists stated in 1996 that TAM time- and dose-dependently increases the relative risk for EC. Overall, there seems to be a two- to threefold increase in the incidence of EC in women treated with adjuvant TAM (ACOG Committee opinion 1996, Love *et al.* 1999), leading to an absolute annual risk of approximately 2 per 1000 patients (Barakat 1999). It is now generally accepted that stage, grade, histological type and other prognostic factors of TAM (20 mg/day)-associated ECs are not different from those of ECs found in the normal population (ACOG Committee opinion 1996, Homesley 1996, Love *et al.* 1999). It is generally accepted that TAM causes endometrial changes (benign polyps and hyperplasia in up to 40% of cases) (ACOG Committee opinion 1996). However, these hyperplasias are often located in the stroma and not in the endometrium (ACOG Committee opinion 1996, Assikis & Jordan 1996, Love *et al.* 1999). Transvaginal ultrasound detected a high incidence (41%) of apparent endometrial thickening in women treated with TAM, although 46% had atrophic endometrium on further assessment, and none of the remaining asymptomatic women had significant lesions (Love *et al.* 1999). Debate, however, continues about the value of screening for EC and of histological evaluation of endometrial abnormalities in women on adjuvant TAM (Barakat 1999, Ramondetta *et al.* 1999).

No increase in EC risk has been observed in adjuvant TAM trials from the UK (Baum 1998) and other countries

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(Creasman 1997). It remains unclear as to whether TAM, because of its estrogen agonistic properties, induces the formation of EC or whether it accelerates the growth of pre-existing EC. A detection bias must also to be taken into account: gynecological symptoms induced by TAM (vaginal discharge, abnormal bleeding) and/or TAM-related ultrasound phenomena ('endometrial thickening') often lead to hysteroscopy, endometrial sampling and/or dilatation and curettage, which might detect latent EC that would not have been found if the woman had not shown these TAM-induced gynecological symptoms (Cohen & Ramahan 1995, Assikis & Jordan 1996, Creasman 1997, Baum 1998).

It has been suggested that TAM might be genotoxic in human endometrium (Hemminki *et al.* 1996), a hypothesis that was not corroborated by findings from analysis of endometrium from patients on TAM in another study (Carmichael *et al.* 1996). The uterine stimulatory effects of a new non-steroidal anti-estrogen, toremifene, seem not to be dissimilar to those of TAM (Tomas *et al.* 1995, Buzdar & Hortobagyi 1998, O'Reagan *et al.* 1998), while the steroidal pure anti-estrogen ICI 182, 780 inhibited the growth of TAM-stimulated human EC in nude mice, in both the presence and the absence of estrogen (O'Reagan *et al.* 1998). The authors concluded that ICI 182, 780 may be safe even if it is used following TAM, and that it may not result in an increased incidence of EC. They considered it possible that ICI 182, 780 may prove useful as an adjuvant agent in early-stage EC (O'Reagan *et al.* 1998). These views, however, have been contested (De Gregorio 1999, Mäenpää *et al.* 1999, Williams 1999).

Raloxifene, a non-steroidal anti-estrogen, which, being a benzothiophene, is chemically distinct from TAM and estradiol, is considered to bind to estrogen receptors and competitively block estrogen-induced DNA transcription in the breast and endometrium (Delmas *et al.* 1997, Cummings *et al.* 1999). So far, in women with osteoporosis using raloxifene (median follow-up, 40 months) neither effects on endometrial thickness nor an increased risk of EC has been observed (Delmas *et al.* 1997, Cummings *et al.* 1999).

Palliative hormonal treatment of invasive EC

Progestogens

For several decades, progestogens have been successfully used in the palliative treatment of advanced or relapsed EC. In early reports, objective response rates of 30–50% have been described, while more recent studies, using strict criteria, found objective response rates of 10–25% (Moore *et al.* 1991, Cohen & Rahaman 1995, Quinn 1999). On the basis of encouraging response rates in breast cancer with high-dose megestrol acetate (MA), the Gynecologic Oncology Group recently performed a phase II trial with 800 mg MA/day in patients with recurrent or advanced ECs. Of 63 patients entered into the trial, 54 were assessible for responses. Of 13 responders (24%), six had a complete response and seven had a partial response. Four of the responses lasted greater than 18 months. Twelve patients (22%) had stable disease. The response rate of patients with grade 1 or 2 lesions (11 of 30, 37%) was significantly higher than that of patients with more poorly differentiated tumors (2 of 24, 8%). Three deaths secondary to cardiovascular events were possibly related to therapy; diabetes was also a contributing factor in all three cases. The authors concluded that high-dose MA is active in endometrial carcinoma but appears to have no advantage over lower-dose progestins (Lentz *et al.* 1996).

These conclusions have been confirmed by another trial, carried out by the Gynecologic Oncology Group, which was published recently (Thigpen *et al.* 1999). Two hundred and ninety-nine eligible women with advanced or recurrent EC were randomized to receive oral medroxyprogesterone acetate (MPA; either 200 mg/day or 1000 mg/day). Of 145 patients receiving the low-dose regimen, there were 25 (17%) complete responses and 11 (8%) partial responses, giving an overall response rate of 25%. The 154 patients receiving the high-dose regimen experienced 14 (9%) complete responses and 10 (6%) partial responses, giving an overall response rate of 15%. The median durations of progression-free survival were 3.2 months and 2.5 months for the low-dose and high-dose regimens respectively. The median survival durations were 11.1 months and 7.0 months respectively. Responses to progestin therapy were more frequent among patients with a well-differentiated histology and a positive PR status (>50 fmol/mg cytosol protein; response rate 37%). Patients with poorly differentiated tumors and/or with PR levels less than 50 fmol/mg cytosol protein had response rates of only 8–9%. Regardless of dose, oral MPA therapy was well tolerated, with thrombophlebitis, the most frequent adverse effect, occurring in only 5% of patients (Thigpen *et al.* 1999). Comparable trials, by the Gynecologic Oncology Group, using cytotoxic drugs resulted in response rates of 22% (doxorubicin) or 30% (doxorubicin plus cyclophosphamide). The median durations of progression-free survival were 3.2 or 3.9 months, and the median survival was 6.9 and 7.3 months respectively (Thigpen *et al.* 1994). In another protocol, the Gynecologic Oncology Group compared doxorubicin with a combination of doxorubicin plus cisplatin, which is considered to be the current cytotoxic regimen of choice (Quinn 1999). In terms of response, the combination yielded a statistically significant superior rate of 44% (which compares with 28% for the single agent). Progression-free survival was also superior for the combination regimen, but overall survival was not significantly different (Thigpen *et al.* 1993, Homesley 1996, Selman *et al.* 1998).

Summarizing the results of their trial on oral MPA, Thigpen and coworkers concluded that this study provides

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no evidence to support the use of 1000 mg MPA per day (orally) instead of 200 mg MPA per day (orally) (Thigpen *et al.* 1999). The use of 200 mg MPA per day (orally) is a reasonable initial approach to the treatment of advanced or recurrent endometrial carcinoma, particularly for those lesions that are well differentiated and/or PR-positive (>50 fmol/mg cytosol protein) (Thigpen *et al.* 1999).

Tamoxifen (TAM)

TAM has been used for the treatment of recurrent or advanced EC at doses of 10–40 mg/day. Response rates varying between 0 and 53% have been described. Of 257 patients treated in several small phase II trials, 56 (22%) had an objective response (Moore *et al.* 1991). TAM has been suggested as an alternative endocrine treatment for EC patients with obesity, hypertension, diabetes, and increased risk for thrombosis, for whom progestin treatment might be harmful. Taking into account the possible potential of TAM to induce EC (see above), this strategy has lost some of its attractiveness.

Both preclinical and clinical data suggest that TAM, when bound to the cytoplasmic ER, can stimulate the production of PRs and therefore, in theory, potentiate the activity of progestin therapy. No significant improvements of the efficacy of progestogen therapy, however, have been achieved by this combination with TAM (Moore *et al.* 1991).

GnRH analogs

Gallagher *et al.* (1991) treated 17 women with recurrent or advanced ECs which were refractory to progestin treatment with the GnRH analogs leuprorelin acetate (7.5 mg/month) or goserelin (3.6 mg/month). Six of these patients (35%) experienced an objective remission which continued for a median of 20 months with no adverse effects (Gallagher *et al.* 1991). In a later update of their series, now comprising 32 patients with recurrent ECs that had progressed through conventional treatment, an objective response was seen in nine patients (28%) with a median duration of 17 months (Jeyarajah *et al.* 1996*b*).

De Vriese and Bonte (1993) treated seven women suffering from advanced ECs with goserelin and achieved two objective remissions. Covens *et al.* (1997) treated 25 patients with recurrent or advanced ECs with leuprorelin acetate (7.5 mg/month) and achieved no objective remission. Markman *et al.* (1997), when treating 9 patients with leuprorelin, also observed no objective response. Given the experimental data on successful growth inhibition of ECs *in vitro* by GnRH analogs (Emons *et al.* 1996, 1997) and the low toxicity of these compounds, it seems appropriate that further clinical trials be undertaken.

Other endocrine treatments of EC

With the use of the aromatase inhibitor aminogluthethimide in 18 women with advanced EC, four objective responses were obtained (Murray & Pitt 1984). One case of successful treatment of a refractory small cell carcinoma of the endometrium with the somatostatin agonist octreotide has been reported (Verschraegen *et al.* 1999).

Primary treatment of early EC with progestins

Some small series have been reported in which grade 1, stage 1 ECs have been successfully treated with progestins alone (for reviews see Kim *et al.* 1997, Randall & Kurman 1997, Quinn 1999). A response rate of 66% has been calculated and 11 pregnancies (two after *in vitro* fertilization) have been reported (Paulson *et al.* 1990, Kim *et al.* 1997, Randall & Kurman 1997, Zuckerman *et al.* 1998). Vinker *et al.* (1999) reported the case of a young nulliparous woman with a well-differentiated adenocarcinoma of the endometrium that did not respond. Upon definite operation (including hysterectomy), a stage II EC was found. These authors point out that the differential diagnosis between a typical hyperplasia and well-differentiated adenocarcinoma is difficult and that a consultation with an endometrial pathologist is needed before a conservative treatment is discussed. In addition, these authors suggest that there might be a publication bias, as only those cases that had favourable outcomes have been reported (Vinker *et al.* 1999). However, older women with well-differentiated ECs and who are unsuitable for surgery or radiotherapy might be good candidates for primary progestin treatment.

Primary endocrine treatment of endometrial hyperplasias

The presence of complex hyperplasia with atypia in the premenopausal woman desirous of fertility poses an enormous problem. Up to 20% of hysterectomy specimens show an invasive carcinoma, one-quarter to one-third of these being associated with myometrial invasion (Quinn 1999). Also, for simple hyperplasia with atypias, a high frequency of malignant transformation must be expected (Kurman *et al.* 1985). A number of reports have attested to the efficacy of progestin treatment (Randall & Kurman 1997, Quinn 1999). They cover, however, only small series and there might be a publication bias. We consider extensive counseling about the risk of the presence of, or the progression to, invasive EC, as well as monitoring of the treatment effect by hysteroscopy and formal dilatation and curettage, as prerequisites of conservative treatment of atypical hyperplasia. Recently, Agorastos *et al.* (1997) have shown that GnRH analogs, which suppress endogenous estrogen, also might be of use in the treatment of endometrial hyperplasias in women who wish to preserve their fertility. These authors also highlight the necessity of endometrial monitoring by formal curettages when complex or atypical

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hyperplasias are treated conservatively (Agorastos *et al.* 1997).

Adjuvant endocrine therapy of EC

Progestins have been used for two decades as adjuvant therapy for ECs that have been treated with a curative intention using surgery and (if indicated) additional radiotherapy (Martin-Hirsch *et al.* 1996). So far, seven randomized trials have been performed on this subject, altogether involving more than 4500 women. Six of these trials (Lewis *et al.* 1974, Malkasian & Decker 1978, MacDonald *et al.* 1988, Vergote *et al.* 1989, De Palo *et al.* 1993, Urbanski *et al.* 1993) have been subjected to a meta-analysis (Martin-Hirsch *et al.* 1996). Although one of the trials had shown a benefit of adjuvant progestin treatment (Urbanski *et al.* 1993), the meta-analysis demonstrated that overall survival was not improved by adjuvant progestogen therapy and even that it might have been adversely affected. Furthermore, this treatment was not associated with any reduction in relapse or death from EC (Martin-Hirsch *et al.* 1996). Most of the EC patients enrolled into these six trials had a low risk of recurrence, so any potential benefits of adjuvant progestin therapy in more severe cases might have been 'diluted' (Martin-Hirsch *et al.* 1996).

In 1998, the COSA-NZ-UK Endometrial Cancer Study Groups published their randomized trial on adjuvant MPA treatment (400 mg/day for 3 years) in 1012 patients with high-risk EC (grade 3 endometrioid, adenosquamous, clear cell or papillary serous cancer, any tumor >1/3 invasive or involving cervix or adnexa). When all patients were analyzed, there were significantly more relapses in patients who did not receive MPA ($P<0.05$), but there were no differences in survival. A secondary analysis, excluding those 112 patients considered ineligible following a central pathology review, was undertaken. Patients who received MPA had a significantly longer disease-free interval ($P=0.03$) and survival ($P=0.03$) than those who did not. Fifty-nine of the 96 women in the control group were given MPA upon relapse. The median survival in this group was 10 months, which compares with 4 months in those patients not given hormonal therapy, a factor that might have reduced the survival benefit of the group treated with MPA from the beginning of the trial. Also of interest was the failure of steroid-receptor status to predict survival advantage in the treatment group. These authors concluded that it seems apparent that the use of adjuvant MPA at this dose and for this length of time has little place in the management of patients with high-risk EC (COSA-NZ-UK Endometrial Cancer Study Groups 1998).

Conclusions

Because of the need for treatment for patients who are often elderly and medically unfit, and the present lack of agents that produce long-lasting responses in EC, future research must evaluate new compounds and approaches.

These treatments ought to include pure anti-estrogens (e.g. ICI 182, 780) and selective ER modulators (e.g. raloxifene and others), to assess whether these compounds are superior to TAM. With the availability of modern, specific and potent aromatase inhibitors (Dowsett 1999), their use in the treatment of EC should be evaluated. The anti-progestin RU 486 has been shown to inhibit EC cell lines *in vitro* at clinically achievable doses (Schneider *et al.* 1998). Intensive preclinical and clinical work is being performed by a number of groups on the application of GnRH-agonists and -antagonists for the treatment of EC (for reviews see Gründker & Emons 1999, Westphalen & Emons 1999). GnRH receptors expressed by more than 80% of ECs might be used for the targeting of cytotoxic drugs (Schally & Nagy 1999). The increasing knowledge on the regulation of EC via peptide hormones, growth factors, steroids and the respective agonistic and antagonistic analogs might open up new therapeutic approaches. In particular, new insights into the molecular mechanisms of steroid hormone action (Enmark & Gustafsson 1998, White & Parker 1998, Jordan & Morrow 1999), together with the development of tissue-specific modulators, might help to overcome the hormone resistance of ECs.

It is to be hoped that ongoing and future research will unravel the molecular mechanisms leading to the formation of virulent type II EC and will thus facilitate the development of efficacious and non-toxic systemic treatment modalities for this disease.

For the time being, progestins are the therapy of choice for patients with atypical endometrial hyperplasia and who wish to preserve their fertility, provided that careful follow-up is guaranteed. For patients with advanced or recurrent EC of a low grade and having positive PRs, progestins are still a reasonable initial approach. So far, neither progestins nor cytotoxic chemotherapy has been shown to have substantial benefits in the adjuvant setting. If the novel endocrine manipulations outlined above (e.g. pure anti-estrogens, selective estrogen receptor modulators, aromatase inhibitors) were shown to be efficacious in the treatment of advanced EC, their usefulness in the adjuvant situation ought to be evaluated.

References

ACOG Committee opinion 1996 Tamoxifen and endometrial cancer. *International Journal of Gynecology and Obstetrics* **53** 197–199.

Agorastos T, Bontis J, Vakiani A, Vuvilis P & Constantinidis T 1997 Treatment of endometrial hyperplasia with gonadotropin releasing hormone agonists: pathological, clinical, morphometric and DNA-cytometric data. *Gynecologic Oncology* **65** 102–114.

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Ambros RA, Sherman ME, Zahn CM, Bitterman P & Kurman RJ 1995 Endometrial intraepithelial carcinoma: a distinctive lesion specifically associated with tumors displaying serous differentiation. *Human Pathology* **26** 1260–1267.

Assikis VJ & Jordan VC 1996 Tamoxifen and endometrial cancer: from experiment to patient. *Recent Results in Cancer Research* **140** 61–71.

Ball HG & Elkadry EA 1998 Endometrial cancer: current concepts and management. *Surgical Oncology Clinics of North America* **7** 271–284.

Barakat RR 1999 Screening for endometrial cancer in the patient receiving tamoxifen for breast cancer (Editorial). *Journal of Clinical Oncology* **17** 1967–1968.

Barakat RR, Park RC, Grigsby PW, Muss HD & Norris HJ 1997 Corpus: epithelial tumors. In *Principles and Practice of Gynecologic Oncology*, edn 2, pp 859–896. Eds WJ Hoskins, CA Perez & RC Young. Philadelphia: Lippincott-Raven.

Baum M 1998 Tamoxifen – the treatment of choice. Why look for alternatives? *British Journal of Cancer* **78** (Suppl 4) 1–4.

Berchuck A & Boyd J 1995 Molecular basis of endometrial cancer. *Cancer* **76** 2034–2040.

Bokhman JV 1983 Two pathogenic types of endometrial carcinoma. *Gynecologic Oncology* **15** 10–17.

Brinton LA & Hoover RN 1997 Epidemiology of gynecologic cancers. In *Principles and Practice of Gynecologic Oncology*, edn 2, pp 3–29. Eds WJ Hoskins, CA Perez & RC Young. Philadelphia: Lippincott-Raven.

Bulun SE, Economos K, Miller D & Simpson ER 1994 CYP 19 (aromatase cytochrome P 450) gene expression in human malignant endometrial tumors. *Journal of Clinical Endocrinology and Metabolism* **79** 1831–1834.

Burke TW & Gershenson DM 1996 Chemotherapy as adjuvant and salvage treatment in women with endometrial carcinoma. *Clinical Obstetrics and Gynecology* **39** 716–727.

Buzdar AU & Hortobagyi GN 1998 Tamoxifen and toremifen in breast cancer: comparison of safety and efficacy. *Journal of Clinical Oncology* **16** 348–353.

Carcangiu ML & Chambers JT 1992 Uterine papillary serous carcinoma: a study of 108 cases with emphasis on the prognostic significance of associated endometrioid carcinoma, absence of invasion, and concomitant ovarian carcinoma. *Gynecology and Oncology* **47** 298–305.

Carmichael PL, Ugwumadu AHN, Neven P, Hewer AJ, Poon GK & Philipps DH 1996 Lack of genotoxicity of tamoxifen in human endometrium. *Cancer Research* **56** 1475–1479.

Chu S, Mamers P, Burger HG & Fuller PJ 2000 Estrogen receptor isoform gene expression in ovarian stromal and epithelial tumors. *Journal of Clinical Endocrinology and Metabolism* **85** 1200–1205.

Cohen CJ & Rahaman J 1995 Endometrial cancer. *Cancer* **76** 2044–2052.

COSA-NZ-UK Endometrial Cancer Study Groups 1998 Adjuvant medroxyprogesterone acetate in high risk endometrial cancer. *International Journal of Gynecological Cancer* **8** 387–391.

Covens A, Thomas G, Shaw P, Ackerman I, Osborne R, Lukka H, Carey M, Franssen E & Roche K 1997 A phase II study of leuprolide in advanced/recurrent endometrial cancer. *Gynecology and Oncology* **64** 126–129.

Creasman W T 1997 Endometrial cancer: incidence, prognostic factors, diagnosis and treatment. *Seminars in Oncology* **24** SI 140–-SI 150.

Creasman W, Odicino F, Maisonneuve P, Benedet J, Shephard J, Sideri M & Pecorelli S 1998 Carcinoma of the corpus uteri (annual report on the results of treatment in gynecological cancer). *Journal of Epidemiology and Biostatistics* **3** 35–61.

Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A & Jordan VC 1999 The effect of raloxifene on risk of breast cancer in postmenopausal women. Results from the MORE randomized trial. *Journal of the American Medical Association* **281** 2189–2197.

Cushing KL, Weiss NS, Voigt L, McKnight B & Beresford SAA 1998 Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. *Obstetrics and Gynecology* **91** 35–39.

Dahia PLM 2000 *PTEN*, a unique tumor suppressor gene. *Endocrine-Related Cancer* **7** 115–129.

De Gregorio MW 1999 Effects of the antiestrogens tamoxifen, toremifene and ICI 182, 780 on endometrial cancer growth. *Journal of the National Cancer Institute* **91** 474–475.

De Palo G, Mangioni C, Periti P, Del Vecchio M & Marubini E 1993 Treatment of FIGO (1971) stage I endometrial carcinoma with intensive surgery, radiotherapy and hormonotherapy according to pathological prognostic groups. Long-term results of a randomized multicenter study. *European Journal of Cancer* **29** 1133–1140.

De Vriese G & Bonte J 1993 Possible role of goserelin, an LHRH agonist, in the treatment of gynecological cancers. *European Journal of Gynaecology and Oncology* **14** 187–191.

Deligdisch L & Cohen CJ 1985 Histologic correlates and virulence implications of endometrial carcinoma associated with adenomatous hyperplasia. *Cancer* **56** 1452–1455.

Deligdisch L & Holinka CF 1986 Progesterone receptors in two groups of endometrial carcinoma. *Cancer* **57** 1385–1388.

Delmas PD, Bjarnason NH, Mitlak BH, Ravoux A-C, Shah AS, Huster WJ, Draper M & Christiansen C 1997 Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *New England Journal of Medicine* **337** 1641–1647.

Dowsett M 1999 Drug and hormone interactions of aromatase inhibitors. *Endocrine-Related Cancer* **6** 181–185.

Emons G, Möller V, Ortmann O, Grossmann G, Trautner U, v. Stuckrad B, Schulz K-D & Schally AV 1996 Luteinizing hormone releasing hormone agonist triptorelin antagonizes signal transduction and mitogenic activity of epidermal growth factor in human ovarian and endometrial cancer cell lines. *International Journal of Oncology* **9** 1129–1137.

Emons G, Ortmann O, Schulz K-D & Schally AV 1997 Growth-inhibiting actions of analogues of luteinizing hormone releasing hormone on tumor cells. *Trends in Endocrinology and Metabolism* **8** 355–362.

Enmark E & Gustafsson J-Å 1998 Estrogen receptor – a novel receptor opens up new possibilities for cancer diagnosis and treatment. *Endocrine-Related Cancer* **5** 213–222.

Gallagher CJ, Oliver RTD, Oram DH, Fowler CG, Blake PR, Mantell BS, Slevin ML & Hope-Stone HF 1991 A new treatment for endometrial cancer with gonadotrophin releasing hormone analogue. *British Journal of Obstetrics and Gynecology* **98** 1037–1041.

Goodman MT, Hankin JH, Wilkens LR, Lyu L-C, McDuffie K, Liu LQ & Kolonel LN 1997 Diet, body size, physical activity,

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and the risk of endometrial cancer. *Cancer Research* **57** 5077–5085.

Grady D, Gebretsadik T, Kerlikowske K, Ernster V & Petiti D 1995 Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstetrics and Gynecology* **85** 304–313.

Gründker C & Emons G 1999 GnRH mechanism of action. In *GnRH Analogues. The State of the Art at the Millennium*, pp 7–29. Ed. B Lunenfeld. New York: Parthenon.

Gründker C, Völker P, Schulz KD & Emons G 2000 Luteinizing hormone-releasing hormone (LHRH) agonist Triptorelin and antagonist Cetrorelix inhibit EGF-induced *c-fos* expression in human gynecological cancers. *Gynecology and Oncology* **78** 194–202.

Gurin CC, Federici MG, Kang L & Boyd J 1999 Causes and consequences of microsatellite instability in endometrial carcinoma. *Cancer Research* **59** 462–466.

Gurpide E 1991 Endometrial cancer: biochemical and clinical correlates. *Journal of the National Cancer Institute* **83** 405–416.

Gusberg SB 1947 Precursors of corpus carcinoma, estrogens and adenomatous hyperplasia. *American Journal of Obstetrics and Gynecology* **54** 905–927.

Gusberg SB 1994 Estrogen and endometrial cancer: an epilogue à la recherche du temps perdu. *Gynecology and Oncology* **52** 3–9.

Hemminki K, Rajaniemi H, Lindahl B & Moberger B 1996 Tamoxifen-induced adducts in endometrial samples from breast cancer patients. *Cancer Research* **56** 4374–4377.

Homesley HD 1996 Management of endometrial cancer. *American Journal of Obstetrics and Gynecology* **174** 529–534.

Horvath G, Leser G, Hahlin M & Henriksson 2000 Exon deletions and variants of human estrogen receptor mRNA in endometrial hyperplasia and adenocarcinoma. *International Journal of Gynecological Cancer* **10** 128–136.

Jeyarajah A, Oram D & Jacobs I 1996*a* Molecular events in endometrial carcinogenesis. *International Journal of Gynecological Cancer* **6** 425–438.

Jeyarajah AR, Gallagher CJ, Blake PR, Oram DH, Dowsett M, Fisher C & Oliver RTD 1996*b* Long-term follow-up of gonadotrophin-releasing hormone analog treatment for recurrent endometrial cancer. *Gynecology and Oncology* **63** 47–52.

Jordan VC & Morrow M 1999 Tamoxifen, raloxifene, and the prevention of breast cancer. *Endocrine Reviews* **20** 253–278.

Kim YB, Holschneider CH, Gosh K, Nieberg RK & Montz FJ 1997 Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. *Cancer* **79** 320–327.

Kleine W, Maier T, Geyer H & Pfleiderer A 1990 Estrogen and progesterone receptors in endometrial cancer and their prognostic relevance. *Gynecology and Oncology* **38** 59–65.

Kumar NS, Ricker J, Owen G, Litman E, Horwitz K & Leslie KK 1998 Selective down-regulation of progesterone receptor isoform B in poorly differentiated human endometrial cancer cells: implications for unopposed estrogen action. *Cancer Research* **58** 1860–1865.

Kurman RJ, Kalminski PF & Norris HJ 1985 The behavior of endometrial hyperplasia: a long term study of 'untreated' hyperplasia in 170 patients. *Cancer* **56** 403–412.

La Vecchia C, Tavani A, Franceseschi S & Parazzini F 1996 Oral contraceptives and cancer. A review of the evidence. *Drug Safety* **14** 260–272.

Lentz SS, Brady MF, Major FJ, Reid GC & Soper JT 1996 High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Journal of Clinical Oncology* **14** 357–361.

Lewis GC, Slack NH, Mortel R & Brass I 1974 Adjuvant progestogen therapy in the definitive treatment of endometrial cancer. *Gynecology and Oncology* **2** 368–376.

Li C, Samsiol G & Iosif C 1999 Quality of life in endometrial cancer survivors. *Maturitas* **31** 227–236.

Liehr JG 2000 Is estradiol a genotoxic mutagenic carcinogen? *Endocrine Reviews* **21** 40–54.

Love CDB, Muir BB, Scrimgeou JB, Leonard RCF, Dillon P & Dixon JM 1999 Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. *Journal of Clinical Oncology* **17** 2050–2054.

Lumbiganon P 1994 Depot-medroxyprogesterone acetate (DMPA) and cancer of the endometrium and ovary. *Contraception* **49** 203–209.

Lupulescu A 1993 Estrogen use and cancer risk: a review. *Experimental and Clinical Endocrinology* **101** 201–214.

Lynch HT, Lynch J, Conway T, Watson P & Coleman RL 1994 Familial aggregation of carcinoma of the endometrium. *American Journal of Obstetrics and Gynecology* **171** 24–27.

MacDonald RR, Thorogod J & Mason MK 1988 A randomized trial of progestogens in the primary treatment of endometrial carcinoma. *British Journal of Obstetrics and Gynecology* **95** 166–174.

MacDonald ND, Salvesen HB, Ryan A, Iversen OE, Akslen LA & Jacobs IJ 2000 Frequency and prognostic impact of microsatellite instability in a large population based study of endometrial carcinomas. *Cancer Research* **60** 1750–1752.

Mäenpää J, Ellmen J, Pasanen T & Kaukonen M 1999 Re: effects of the antiestrogens tamoxifen, toremifene and ICI 182, 780 on endometrial cancer growth. *Journal of the National Cancer Institute* **91** 972–973.

Malkasian GD & Decker DG 1978 Adjuvant progesterone therapy for stage I endometrial carcinoma. *International Journal of Gynecology and Obstetrics* **16** 48–49.

Markman M, Kennedy A, Webster K, Peterson G, Kulp B & Belinson J 1997 Leuprolide in the treatment of endometrial cancer. *Gynecology and Oncology* **66** 542.

Martin-Hirsch PL, Lilford RJ & Jarvis GJ 1996 Adjuvant progestogen therapy for the treatment of endometrial cancer: a review and meta-analysis of published randomized controlled trials. *European Journal of Obstetrics and Gynecology and Reproductive Biology* **65** 201–207.

Maxwell GL, Risinger JI, Gumbs C, Shaw H, Bentley RC, Barrett AB & Futreal PA 1998 Mutation of the *PTEN* tumor suppressor gene in endometrial hyperplasia. *Cancer Research* **58** 2500–2503.

Moll U, Chalas E, Auguste M, Meany P & Chumas J 1996 Uterine papillary serous carcinoma evolves via a p 53–driven pathway. *Human Pathology* **27** 1295–1300.

Moore TD, Phillips PH, Nerenstone SR & Cheson BD 1991 Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. *Journal of Clinical Oncology* **9** 1071–1088.

Murray RML & Pitt P 1984 Treatment of advanced metastatic breast cancer, carcinoma of the prostate and endometrial cancer with aminoglutethimide. In *Aminoglutethimide as an Aromatase Inhibitor in the Treatment of Cancer*, pp 109–122. Eds GA Nagel & RJ Santen. Bern: Huber.

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Mutter GL, Chaponot ML & Fletcher JA 1995 A polymerase chain reaction assay for non-random X chromosome inactivation identifies monoclonal endometrial cancers and precancers. *American Journal of Pathology* **146** 501–508.

Mutter GL, Boyton KA, Faquin WC, Ruiz RE & Jovanovic AS 1996 Allelotype mapping of unstable microsatellites establishes direct lineage continuity between endometrial precancers and cancer. *Cancer Research* **56** 4483–4486.

Mutter GL, Lin MC, Fitzgerald JT, Keim JB, Baak JPA, Lees JA, Weng L-P & Eng C 2000 Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. *Journal of the National Cancer Institute* **92** 924–931.

Nagamani M & Stuart CA 1998 Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. *American Journal of Obstetrics and Gynecology* **179** 6–12.

Nagamani M, Hannigan EV, Dink VT & Stuart C 1988 Hyperinsulinemia and stromal luteinization of the ovaries in postmenopausal women with endometrial cancer. *Journal of Clinical Endocrinology and Metabolism* **67** 144–148.

Nagamani M, Stuart CA & Doherty MG 1992*a* Increased steroid production by the ovarian stromal tissue of postmenopausal women with endometrial cancer. *Journal of Clinical Endocrinology and Metabolism* **74** 172–176.

Nagamani M, Doherty MG, Smith ER & Chandrasekhar Y 1992*b* Increased bioactive luteinizing hormone levels in postmenopausal women with endometrial cancer. *American Journal of Obstetrics and Gynecology* **167** 1825–1830

Niederacher D, An H-X, Camrath S, Dominik SI, Göhring UJ, Oertel A, Grass M, Hantschmann P, Lordnegad MR & Beckmann MW 1998 Loss of heterozygosity of BRCA1, TP53 and TCRD markers analysed in sporadic endometrial cancer. *European Journal of Cancer* **34** 1770–1776.

Niederacher D, An H-X, Cho Y-J, Hantschmann P, Bender HG & Beckmann MW 1999 Mutations and amplification of oncogenes in endometrial cancer. *Oncology* **56** 59–65.

Nyholm HCJ, Nielsen AL, Lyndrup J, Norup P & Thorpe SM 1992 Biochemical and immunohistochemical estrogen and progesterone receptors in adenomatous hyperplasia and endometrial carcinoma: correlations with stage and other clinicopathologic features. *American Journal of Obstetrics and Gynecology* **167** 1334–1342.

Nyholm HCJ, Nielsen AC & Norup P 1993*a* Endometrial cancer in postmenopausal women with and without previous estrogen replacement treatment: comparison of clinical and histopathological characteristics. *Gynecology and Oncology* **49** 229–235.

Nyholm HC, Nielsen AL, Lyndrup J, Dreisler A, Hagen C & Haug E 1993*b* Plasma oestrogens in postmenopausal women with endometrial cancer. *British Journal of Obstetrics and Gynecology* **100** 1115–1119.

O'Reagan RM, Cisneros A, England GM, MacGregor JI, Muenzner HD, Assikis VJ, Bilimora MM, Piette M, Dragan YP, Pitot HC, Chatterton R & Jordan VC 1998 Effects of the antiestrogens tamoxifen, toremifene and ICI 182, 780 on endometrial cancer. *Journal of the National Cancer Institute* **90** 1552–1558.

Parazzini F, La Vecchia C, Bocciolone L & Francheschi S 1991 The epidemiology of endometrial cancer. *Gynecology and Oncology* **41** 1–16.

Parazzini F, La Vecchia C, Negri E, Moroni S & Chatenoud L 1995 Smoking and risk of endometrial cancer: results from an Italian case-control study. *Gynecology and Oncology* **56** 195–199.

Paulson RJ, Saure MV & Lobo PA 1990 Pregnancy after *in vitro* fertilization in a patient with stage I endometrial carcinoma treated with progestins. *Fertility and Sterility* **54** 735–736.

Pike MC, Peters RK, Cosen W, Probst-Hensch NM, Felix JC, Wan PC & Mack TM 1997 Estrogen-replacement therapy and endometrial cancer. *Journal of the National Cancer Institute* **89** 1110–1116.

Podratz KC, Mariani A & Webb MJ 1998 Staging and therapeutic value of lymphadenectomy in endometrial cancer (Editorial). *Gynecology and Oncology* **70** 163–164.

Quinn MA 1999 Hormonal treatment of endometrial cancer. *Hematology/Oncology Clinic of North America* **13** 163–187.

Ramondetta LM, Sherwood JB, Dunton CJ & Palazzo JP 1999 Endometrial cancer in polyps associated with TAM use. *American Journal of Obstetrics and Gynecology* **180** 340–341.

Randall TC & Kurman RJ 1997 Progestin treatment of atypical hyperplasia and well differentiated carcinoma of the endometrium in women under age 40. *Obstetrics and Gynecology* **90** 434–440.

Reynolds RK, Hu C & Baker VV 1998 Transforming growth factor- and insulin-like growth factor-I but not epidermal growth factor elicit autocrine stimulation of mitogenesis in endometrial cancer cell lines. *Gynecology and Oncology* **70** 202–209.

Risinger JI, Hayes AK, Berchuk A & Barrett JC 1997 PTEN/MMAC1 mutations in endometrial cancers. *Cancer Research* **57** 4736–4738.

Saegusa M & Okayasu I 2000 Changes in expression of estrogen receptors alpha and beta in relation to progesterone receptor and PS 2 status in normal and malignant endometrium. *Japanese Journal of Cancer Research* **91** 510–518.

Schally AV & Nagy A 1999 Cancer chemotherapy based on targeting cytotoxic peptide conjugates to their receptors on tumors. *European Journal of Endocrinology* **141** 1–14.

Schneider CC, Gibb RK, Taylor DD, Wan T & Gercel-Taylor C 1998 Inhibition of endometrial cancer cell lines by Mifepristone (RU 486). *Journal of the Society for Gynecologic Investigation* **5** 334–338.

Selman AE, Fowler JM, Martinez-Monge R & Copeland LJ 1998 Doxorubicin and/or cisplatin based chemotherapy for the treatment of endometrial carcinoma with retroperitoneal lymph node metastases. *International Journal of Gynecologic Cancer* **8** 423–429.

Shapiro JA, Weiss NS, Beresford SAA & Voigt LF 1998 Menopausal hormone use and endometrial cancer by tumor grade and invasion. *Epidemiology* **9** 99–101.

Sherman ME 2000 Theories of endometrial carcinogenesis: a multidisciplinary approach. *Modern Pathology* **13** 295–308.

Sherman ME, Bur ME & Kurman RJ 1995 P 53 in endometrial cancer and its putative precursors: evidence for diverse pathways of tumorigenesis. *Human Pathology* **26** 1268–1274.

Sherman ME, Sturgeon S, Brinton LA, Potischman N, Kurman RJ, Berman ML, Mortel R, Twiggs LB, Barrett RJ & Wilbanks JD 1997 Risk factors and hormone levels in patients with serous and endometrial uterine carcinomas. *Modern Pathology* **10** 963–968.

Sivridis E, Fox H & Buckley CH 1998 Endometrial carcinoma: two or three entities? *International Journal of Gynecologic Cancer* **8** 183–188.

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Tashiro H, Isacson C, Levine R, Kurman RJ, Cho KR & Hedrick L 1997 P 53 gene mutations are common in uterine serous carcinoma and occur early in their pathogenesis. *American Journal of Pathology* **150** 188–185.

Terakawa N, Harada T, Minagawa Y, Kigawa J & Sato B 1996 Endometrial cancer. In *Hormone-dependent Cancer*, pp 477–498. Eds JR Pasqualini & BS Katzenellenbogen. New York: Marcel Dekker.

Terry P, Baron JA, Weiderpass, E, Yuen J, Lichtenstein P & Nyren O 1999 Lifestyle and endometrial cancer risk: a cohort study from the Swedish twin registry. *International Journal of Cancer* **82** 38–42.

Thigpen J, Blessing H, Homesley H, Malfetano J, DiSaia PJ & Yordan E 1993 Phase III trial of doxorubicin +/- cisplatin in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group (GOG) study. *Proceedings of the American Society for Clinical Oncology* **12** 261.

Thigpen JT, Blessing JA, DiSaia PJ, Yordan E, Carson LF & Evers C 1994 A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Journal of Clinical Oncology* **12** 1408–1414.

Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, Soper JT & Given FT 1999 Oral medroxy-progesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose–response study by the Gynecologic Oncology Group. *Journal of Clinical Oncology* **17** 1736–1744.

Tomas E, Kauppila A, Blanco G, Apaya-Sarkkinnen M & Laatikainen T 1995 Comparison between the effects of tamoxifen and toremifene on the uterus in postmenopausal breast cancer patients. *Gynecology and Oncology* **59** 261–266.

Troisi R, Potischman N, Hoover RN, Siiteri P & Brinton LA 1997 Insulin and endometrial cancer. *American Journal of Epidemiology* **146** 476–482.

Urbanski K, Karolewski K, Kojs Z, Klimek M & Dyba T 1993 Adjuvant progestogen therapy improves survival in patients with endometrial cancer after hysterectomy. Results of a one-institutional prospective clinical trial. *European Journal of Gynecology and Oncology* **14** (Suppl) 98–104.

Vasen HFA, Watson P, Mecklin JP, Jass JR, Green JS, Nomizu T, Möller H & Lynch HT 1994 The epidemiology of endometrial cancer in hereditary non-polyposis colorectal cancer. *Anticancer Research* **14** 1675–1678.

Vergote I, Kjorstad K, Abeler V & Kolstad P 1989 A randomized trial of adjuvant progestogen in early endometrial cancer. *Cancer* **64** 1011–1016.

Verschraegen CF, Matei C, Loyer E, Malpica A, Tornoss C, Kudelka AP & Kavanagh JJ 1999 Octreotide induced remission of a refractory small cell carcinoma of the endometrium. *International Journal of Gynecologic Cancer* **9** 80–85.

Vinker S, Shani A, Open M, Fenig E & Dgani R 1999 Conservative treatment of adenocarcinoma of the endometrium in young patients. Is it appropriate? *European Journal of Obstetrics and Gynecology and Reproductive Biology* **83** 63–65.

Watanabe K, Sasano H, Harada N, Ozaki M, Niikura H, Sato S & Yajima A 1995 Aromatase in human endometrial carcinoma and hyperplasia. Immunohistochemical, *in situ* hybridization, and biochemical studies. *American Journal of Pathology* **146** 491–500.

Weiderpass E, Adami H-O, Baron JA, Magnusson C, Bergström R, Lindgren A, Correia N & Persson I 1999*a* Risk of endometrial cancer following estrogen replacement with and without progestins. *Journal of the National Cancer Institute* **91** 1131–1137.

Weiderpass E, Baron JA, Adami H-O, Magnusson C, Lindgren A, Bergström R, Correia N & Persson I 1999*b* Low-potency oestrogen and risk of endometrial cancer: a case control study. *Lancet* **353** 1824–1828.

Westphalen S & Emons G 1999 GnRH analogues in ovarian, breast and endometrial cancers. In *GnRH Analogues. The State of the Art at the Millennium*, pp 105–120. Ed. B. Lunenfeld. New York: Parthenon.

White R & Parker MG 1998 Molecular mechanisms of steroid hormone action. *Endocrine-Related Cancer* **5** 1–14.

Williams G M 1999 Re: effects of the antiestrogens tamoxifen, toremifene and ICI 182, 780 on endometrial cancer growth. *Journal of the National Cancer Institute* **91** 722–723.

Zuckerman B, Lavie O, Neuman M, Rabinowitz R, Ben-Chetrit A, Voss E, Rosenmann E & Beller V 1998 Endometrial carcinoma stage I grade II. Conservative treatment followed by healthy term pregnancy. *International Journal of Gynecological Cancer* **8** 172–176.

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