The pathogenesis of endometrial carcinomas at menopause: facts and figures

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ABSTRACT

Almost a third of the life of a woman is now postmenopausal, and during this period over 80% of endometrial carcinomas develop. This is by far the most common gynaecological malignancy in the industrialised world and, probably, the less completely understood with regard to its pathogenesis after the menopause. For while it is generally thought that these neoplasms are non-oestrogen-induced, we are, at the same time, informed that oestrogenic stimulation is continuous during menopause through increases to oestrone formation in the adipose tissue from androgens of adrenal and ovarian origin. Furthermore, the postmenopausal endometrium has been typified as atrophic, which is indeed true, but is also implied as being inactive, which in fact it is not; in most cases, the postmenopausal endometrium appears to be weakly proliferative with potential to give rise to an endometrial carcinoma. It is also assumed that postmenopausal endometrial tumours are predominantly of serous papillary and clear cell type, and, in general, they are not well-differentiated endometrioid carcinomas; in reality, no more than 15% are serous papillary and clear cell carcinomas, and no less than 55% are well-differentiated endometrioid neoplasms. The overall prognosis is presumed to be poor, yet postmenopausal patients harbouring well-differentiated endometrioid carcinomas have the same excellent prognosis as those premenopausal women having endometrioid tumours of similar grade and stage. This brief account of endometrial carcinogenesis at menopause re-evaluates these issues and, in the light of new and old evidence, proposes the separation of G1 endometrioid adenocarcinomas (low-grade tumours) from all others (high-grade tumours).

INTRODUCTION

The study of endometrial carcinoma at menopause presents an interesting challenge. The tumour is, on the whole, the commonest gynaecological malignancy in the industrialised world, comprising 4% of all cancers in women, and a lifetime risk of 2–3%. It is a disease of ageing, with over 80% of cases occurring during the menopause. This is a paradox, for endometrial carcinomas are hormone-dependent tumours and, as such, have been associated with high circulating levels of unopposed oestrogens (oestrogens in the absence of progesterone). Yet, at the time these tumours most commonly occur, that is during menopause, oestrogen secretion is waning. To acknowledge that prolonged oestrogenic stimulation of the endometrium occurs in carcinomas developing in the young (type I carcinomas), while postmenopausal women simply lack such a stimulus (type II carcinomas), would have us understand not what the mechanism of the disease is in older women, but what it is not.

As a consequence of ovarian failure, endometrial carcinomas during menopause have been presumed to originate from a background of endometrial atrophy and inactivity. There is little doubt that the postmenopausal endometria are atrophic, but this does not necessarily mean that they are also inactive—a contention that needs further thought. How could a state of ‘inertia’ give rise to a new growth, even if this is an abortive growth? It is true that serous papillary and clear cell carcinomas, which are hosted almost exclusively by the postmenopausal uteri, are lethal tumours. The question remains, of course, how prevalent these tumours are to affect an overall prognosis? And what is the frequency of other postmenopausal endometrial tumours that are known to have a much better outcome? These are issues that are becoming increasingly important.

This review will focus on endometrial carcinomas developing during menopause, not simply because they are more common, but because their pathogenesis is less completely understood; the pathogenesis of tumours arising in young women during their reproductive years has been precisely delineated and requires no further consideration.

PATHOGENETIC MECHANISM IN ENDOMETRIAL CARCINOMAS AT MENopause: YET AGAIN, AN OESTROGENIC MILIEU

The belief that postmenopausal endometrial carcinogenesis is not oestrogen induced rests largely upon the paucity of ovarian function that follows the menopause and the presence of a thin atrophic endometrium. This may all be true, but should not be allowed to detract from the fact that oestrogen production continues after the menopause. For indeed, in addition to oestrogens being secreted by the developing ovarian follicle during reproductive life, they are also secreted during the menopause from androgens produced by the adrenal glands and the non-specialised ovarian stroma. The secretion, mainly in the form of androstenedione and testosterone, is increased notably during this period, in parallel with an increased conversion of androgens to oestrone.
biologically active hormones, as they are unbound to sex-hormone-binding globulin.\textsuperscript{20–30} This is because the level of sex-hormone-binding globulin is decreased in obese postmenopausal women.\textsuperscript{15} 30–36 It is worth mentioning that although all postmenopausal women are capable of converting androgens to oestrogens under ‘physiological’ conditions,\textsuperscript{37} only those that have a high efficiency in doing so are at risk of developing endometrial cancer\textsuperscript{38 39}; indeed, extrafollicular oestrogen concentrations are significantly higher in women with endometrial carcinomas relative to healthy controls.\textsuperscript{22 26 34} It is possible that some of the conversion occurs in the endometrium, through endometrial aromatase cytochrome P450, thus increasing oestrogen concentrations at the endometrial level.\textsuperscript{21 40}

The mechanism of conversion of androgen to oestrogen assumes a dominant role under the pathological conditions of oestrogen-secreting ovarian neoplasms, mainly granulosa and thecal cell tumours, and in a background of cortical stromal hyperplasia and hyperthecosis.\textsuperscript{21 41} Nulliparity or low parity, which is associated with failure of ovulation, and persistence of the mature follicle and prolonged high oestrogen levels without corpus luteum formation, may enhance the possibility of developing endometrial carcinoma by increasing the exposure time of the endometrium to endogenous oestrogens.\textsuperscript{42}

It is, however, only the therapeutic intervention in the uterus, specifically in the form of hormone replacement therapy, which illustrates clearly the role of oestrogens in postmenopausal endometrial carcinogenesis.\textsuperscript{35 38 41–47} This practice, which simulates precisely the naturally occurring ‘prolonged oestrogenic stimulation of the endometrium, unopposed by progestosterone action’, has been associated with an 8-fold to 15-fold increase in incidence of endometrial carcinoma.\textsuperscript{48–53} Most interestingly, the risk was reduced considerably with the addition of progestins.\textsuperscript{45 54–56}

It is thus apparent that an oestrogenic milieu does exist in the postmenopausal endometrium and may account, to a certain extent, for the observed increases of endometrial cancer in older women.\textsuperscript{54 56 57} Obesity, as the driving force of the conversion mechanism, has been implicated in about 40% of all endometrial cancer cases in postmenopausal women.\textsuperscript{58–62} Notably, oestrone and oestriol concentrations have been shown to be significantly higher in women with endometrial cancer compared with healthy women, and also in endometrial carcinoma cell lines compared with unaffected controls.\textsuperscript{50} Oestrone, while a weak oestrogen, has proved to be more effective than oestradiol and oestriol in promoting endometrial carcinomas in mice.\textsuperscript{64}

THE DYNAMICS OF AN ATROPHIC, BUT PROLIFERATING/NON-INACTIVE POSTMENOPAUSAL ENDOMETRIUM

Oestrogen drive stimulation appears to be a common pathogenetic mechanism in postmenopausal endometrial carcinomas, particularly when it acts continuously and in relatively increased concentrations on its target tissue: the endometrium.\textsuperscript{42} 35 38 59 65

But what are the changes that a ‘physiological’ uterine mucosa assumes following the decline of ovarian function?

At first, the non-cycling, yet normal, asymptomatic postmenopausal endometrium becomes gradually atrophic, assuming a shallow uterine mucosa, 2.2 mm thick, with loss of distinction between the basal layer and the functional layer.\textsuperscript{65}

The endometrial glands may initially retain some proliferative activity, albeit weak,\textsuperscript{65–67} but, with further decline of oestrogen secretion, the uterine mucosa becomes functionally inactive.\textsuperscript{65} It is composed of small tubular glands, widely spaced, and these are lined by cuboidal indeterminate epithelium, showing neither secretory nor proliferative activity; the stroma is dense and fibrous. Finally, with complete absence of ovarian function,\textsuperscript{68} the endometrium falls into cystic atrophy,\textsuperscript{69} having a thin uterine mucosa, cystically dilated endometrial glands, and a flattened inactive epithelium.

The loss of the negative feedback of oestrogens on the hypothalamus, combined with the loss of the restraining action of inhibin B on the secretion of follicle-stimulating hormone, provoke a marked increase in serum gonadotropins, predominantly pituitary follicle stimulating hormone.\textsuperscript{70–72} This, in turn, stimulates the production of androgens, mainly androstenedione and testosterone, by the non-specialised ovarian stroma. Peripheral conversion of oestrogen and androgen to oestrone through aromatisation in the adipose tissues becomes the primary source of endogenous oestrogens in postmenopausal women and may be sufficient to stimulate the endometrium.\textsuperscript{59}

Subject to these conditions, the endometrium, while remaining atrophic, abandons its state of inertia and resumes its weak proliferative activity,\textsuperscript{66 67 75} exemplified by focal proliferation of endometrial glands, with moderate tortuosity, pseudosтратification and infrequent mitoses.

It is true that endometrial carcinomas occurring during the reproductive years are all, or nearly all, well-differentiated endometrioid adenocarcinomas (so-called type I carcinomas). However, the reverse contention may not be necessarily correct as, indeed, only a quarter of the tumours developing after the menopause are endometrioid adenocarcinomas.\textsuperscript{81} (box 1).

THE PREVALENCE OF THE VARIOUS TUMOUR CELL TYPES: A CLASSIFICATION SCHEME WITH PROGNOSTIC VALUE

It is true that endometrial carcinomas occurring during the reproductive years are all, or nearly all, well-differentiated endometrioid adenocarcinomas (so-called type I carcinomas). However, the reverse contention may not be necessarily correct as, indeed, only a quarter of the tumours developing after the menopause are non-endometrioid carcinomas. In addition, it is not always realised that as many as 55% of endometrial carcinomas at menopause are also of the G1 endometrioid type, (figure 1A) and a further 20% are G2/G3 endometrioid tumours (figure 1B).\textsuperscript{5 15 73 80 81} The prototype of non-endometrioid carcinomas (type II carcinomas), the serous papillary (figure 1C) and the clear cell (figure 1D) tumours, share no more than 15% of the total,\textsuperscript{13 14 82–86} and there is, of course, a group of around 10% of rather unusual types of non-endometrioid carcinomas.\textsuperscript{81} (box 1).
Obviously, these data have an impact on patient survival. The many well-differentiated endometrioid adenocarcinomas originating from an atrophic postmenopausal endometrium are similar in all respects to those endometrioid adenocarcinomas of equal grade and stage that are associated with atypical hyperplasia in young premenopausal women; they all have an almost excellent prognosis, with reported 5-year survival rates varying from 87% to 97%. The serous papillary and clear cell carcinomas, on the other hand, are aggressive tumours that have an increased metastatic potential, high tendency for relapses, and a 5-year survival rate that may be as low as 15%.

Recently, Soslow et al who investigated a series of high-grade endometrial neoplasms of different histological type, namely G3 endometrioid, serous papillary and clear cell carcinomas, found that they were all associated with an almost similar clinical outcome; the corresponding 5-year survival rates of 45%, 36% and 50% were not statistically significant.

There can be no doubt that a diverse collection of lethal tumours, such as the serous papillary, the clear cell, other non-endometrioid tumours, together with the G2/G3 endometrioid carcinomas, would make the survival of postmenopausal women worse. Yet, it has to be admitted that these tumours attracted a degree of attention disproportionate to their frequency, while the many well-differentiated endometrioid adenocarcinomas of the postmenopausal age, with an unquestionably favourable prognosis, have been almost totally ignored.

Thus, the longstanding assertion that endometrial carcinomas developing during menopause are of poor prognosis is too wide a generalisation.

It has been thus far illustrated that endometrial carcinomas occurring at menopause form a heterogeneous group of tumours, the prognosis of which depends on the histological type (whether endometrioid or non-endometrioid) (box 1) and on the degree of differentiation (whether G1, G2 or G3) (box 2). However, grading of endometrioid adenocarcinomas can be highly subjective, particularly in distinguishing between...
International Federation of Gynecology and Obstetrics (FIGO) grade G1 (<5% solid growth) and FIGO G2 (>5% solid growth) tumours are considered grade 3; adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component. *Notes on FIGO grading: notable nuclear atypia, inappropriate for the architectural grade (particularly pleomorphism and prominent nuclei), raises the grade from 1 to 2 or from 2 to 3 [146]; by convention, serous papillary and clear cell carcinomas are considered grade 3; adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component. †High grade if at least two of the three criteria are present. ‡Irrespective of squamous or non-squamous differentiation.

Table 1 Specific features of low-grade and high-grade endometrial carcinomas developing during menopause

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low-grade endometrial carcinoma</th>
<th>High-grade endometrial carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Perimenopausal and postmenopausal years</td>
<td>Perimenopausal and postmenopausal years</td>
</tr>
<tr>
<td>Tumour-free endometrium adjacent to carcinoma</td>
<td>Atrophic (but not inactive); usually weakly proliferative</td>
<td>Atrophic (but inactive); usually weakly proliferative</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Extra-ovarian oestrione stimulation</td>
<td>Extra-ovarian oestrione stimulation</td>
</tr>
<tr>
<td>Frequency</td>
<td>Common (about 55%)</td>
<td>Less common (about 45%)</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>Rarely, but if present: atypical endometrial hyperplasia</td>
<td>Presumed to be less uncommon: endometrial intraepithelial carcinoma/endometrial glandular dysplasia (p53 signatures*)</td>
</tr>
<tr>
<td>Histological type</td>
<td>Endometrioid carcinoma G1 (55%), mucinous carcinoma G1</td>
<td>Serous papillary carcinoma (10%), clear cell carcinoma (5%), endometrioid carcinoma G2/G3 (20%), non-endometrioid carcinoma (10%)</td>
</tr>
<tr>
<td>Differentiation</td>
<td>G1</td>
<td>G2–G3</td>
</tr>
<tr>
<td>Receptor state</td>
<td>ER rich, PR rich</td>
<td>ER rich or PR poor</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Nil to inner 1/3</td>
<td>Inner 1/3 to 3/3</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>Less common</td>
<td>Common</td>
</tr>
<tr>
<td>Stage</td>
<td>I</td>
<td>I–IV</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Almost excellent</td>
<td>Poor</td>
</tr>
</tbody>
</table>

*ER, oestrogen receptor; PR, progesterone receptor.

Box 2 The three-level FIGO grading system for endometrial adenocarcinomas of the endometrioid cell type compared with proposed binary tumour grading systems

1988 FIGO grading [146]

- G1: composed almost exclusively of well-formed glands; ≤5% solid (non-squamous) component
- G2: 6–50% solid (non-squamous) component
- G3: >50% solid (non-squamous) component; lacks well-formed glands

Taylor et al. (1999) [112]

- Low grade: ≤20% solid (non-squamous) growth
- High grade: >20% solid (non-squamous) growth

Lax et al. (2000) [111]

- Low grade: ≤50% solid growth†; expansive/pushing tumour border, no evidence of tumour cell necrosis
- High grade: >50% solid growth†; infiltrative growth pattern, tumour cell necrosis

Scholten et al. (2004) [110]

- Low grade: ≤50% solid growth‡
- High grade: >50% solid growth‡

Alkushi et al. (2005) [109]

- Low grade: predominance of glandular pattern, mild to moderate atypia, ≤6 mitoses per HPF
- High grade: Predominance of papillary or solid growth, severe nuclear atypia, >6 mitoses per HPF

FIGO, International Federation of Gynecology and Obstetrics; HPF, high-power field.

GENETIC SUBGROUPS OF ENDOMETRIAL CARCINOMA: WHAT IS THE MESSAGE?

Our option to separate G1 endometrioid adenocarcinomas from those of G2/3 and the non-endometrioid tumours appears to be also justified in terms of molecular genetic changes. In the first instance, it was shown that endometrioid and serous papillary carcinomas express genetic aberrations with different frequencies (table 2). The endometrioid adenocarcinomas display, as a whole, a high incidence of mutations in the PTEN [117–120] and K-ras genes [121–123] and often contain microsatellite instability [124–127] and a near diploid karyotype [128–130]. In contrast, the serous papillary carcinomas rarely, if ever, exhibit PTEN and K-ras mutations, microsatellite instability or a diploid karyotype, but are more likely to have p53 mutations [122, 131–135] and a non-diploid (aneuploid) karyotype [128–130].

There has been some evidence, however, that in addition to such genetic differences existing between various types of endometrial carcinoma (ie, serous papillary versus

a binary grading system that divides endometrial tumours into low-grade and high-grade is more effective in assessing prognosis and has greater reproducibility than the presently used three-tier FIGO grading system. This has been claimed for all two-tier grading systems proposed [108–112] whether based solely on the proportion of solid growth [110–112] or on solid growth and additional histological criteria, such as mode of invasion and tumour cell necrosis [111] or nuclear atypia and mitotic activity [109] (box 2) (for a full discussion, see the recent review by Clarke and Gilks [105]).

In this context, the endometrial carcinomas may be conveniently divided, in terms of prognosis, into groups of low-grade and high-grade. The first, and apparently larger, group of tumours is represented by the well-differentiated endometrioid carcinomas and the mucinous tumours; the mucin-secreting adenocarcinomas have a remarkable resemblance to G1 endometrioid neoplasms, and occur with a frequency of 0.6% to 5% [67] and a 5-year survival rate of 95%. [101] 113–116 The second group of endometrial carcinomas comprises the high-grade serous papillary and the clear cell carcinomas, the G2 and G3 endometrioid neoplasms, and the various unusual types of non-endometrioid carcinomas. This system is meant to be prognostically meaningful and may lead to individualisation of treatment. Box 1 outlines the taxonomic scheme proffered, and table 1 summarises the specific features of the various tumours.
endometrioid), they also exist between the various grades of endometrioid neoplasms. For example, the high-grade endometrioid carcinomas tend to follow the molecular patterns expressed by the serous papillary carcinomas rather than those of low-grade endometrioid neoplasms. More specifically, p53 mutations have been reported to occur in 93% of serous papillary carcinomas, but in only 17% of endometrioid carcinomas. Yet, endometrioid carcinomas, assessed by tumour grade, have been found to express p53 mutations only if they are high-grade: G3, 43%; G2, 8%; G1, 0%.134 136 In another study, p53 mutations were recorded in 82% of serous papillary carcinomas, 57% in G3 endometrioid disease, and 14% in the combined group of G1/G2 endometrioid carcinomas.134

It is worth noting that p53 defects were less frequent in clear cell carcinomas than in serous papillary tumours,134 and any difference in p53 expression between clear cell and G3 endometrioid carcinomas was not statistically significant.134 This tendency was repeated by immunohistochemistry. Over-expression of p53 was more frequent in non-endometrioid than in endometrioid carcinomas (38% versus 13%, respectively); however, when endometrioid carcinomas were assessed as a function of tumour differentiation, the G3 endometrioid carcinomas almost reached the frequency of the non-endometrioid tumours (56% versus 38%); the reported values for G2 and G1 endometrioid carcinomas were 20% and 8%, respectively.137

Likewise, the genetic aberrations have been found to be more frequent and more complex in serous papillary than in endometrioid carcinomas, with means of 5.7 versus 1.5 aberrations per tumour, respectively.138 However, when endometrioid carcinomas were assessed as a function of tumour grade, the mean numbers of changes per sample were 2.3 for G3, 2.2 for G2, and 0.73 for G1 carcinomas.

E-cadherin, which is generally considered as a suppressor of tumour progression,139–141 has been found to be associated with reduced expression in serous papillary, clear cell and the G3 endometrioid carcinomas, when the latter were evaluated by tumour grade.124–144

Similar trends have been manifested in ploidy-related parameters. Thus, the proportion of non-diploid karyotypes in various studies ranged from 70–95% in serous papillary carcinomas, and from 24–70% in G3 endometrioid carcinomas128–130; in fact, the highest values of G3 endometrioid tumours have been identified with the lowest values of serous papillary carcinomas. The corresponding figures for G2 and G1 endometrioid carcinomas were 11–14% and 9–11%, respectively.128 130

Others have found that G3 endometrioid carcinomas may even exceed the serous papillary carcinomas in frequency of ploidy-related parameters; tetraploidy, for example, has been reported as being expressed in 21% of G3 endometrioid carcinomas versus 18% of serious papillary tumours.130 The corresponding tetraploid values for G2 and G1 endometrioid carcinomas were 5% and 3%, respectively.130 It appears, therefore, that the proposed taxonomy for endometrial carcinomas has considerable merit in this respect.

**CONCLUDING REMARKS**

Despite the decline in ovarian function that follows menopause, oestrogen, but not progesterone, synthesis continuous during the postmenopausal years through increases to oestrogen formation from androgens of adrenal and ovarian origin. The reaction, which occurs in the adipose tissue and enhances with increasing body weight and advanced age, may occasionally produce relatively high oestrogen concentrations.

Under such conditions, the endometrium, while remaining thin and atrophic, assumes a weak proliferative activity, which is capable of giving genesis to various forms of proliferation and potentially to endometrial carcinoma. Indeed, there is a dramatic increase in the incidence of endometrial carcinoma during the postmenopausal years; this may suggest that oestrone, a weak oestrogen, may play the same pathogenetic role in the development of endometrial carcinoma as does a potent oestrogen, oestradiol, in young premenopausal women. If this is true, as it appears, endometrial carcinomas should no longer be regarded as ‘oestrogen dependent’ (type I carcinomas occurring in premenopausal women) or ‘oestrogen independent’ (type II carcinomas developing at menopause), but rather as neoplasms of having varying degrees of hormone dependence.

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**Table 2 The main gene expression profiles in endometrioid and serous papillary carcinomas of the endometrium**

<table>
<thead>
<tr>
<th></th>
<th>Endometrioid carcinoma (%)</th>
<th>Serous papillary carcinoma (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN mutations</td>
<td>37–83</td>
<td>0–5</td>
<td>117–120</td>
</tr>
<tr>
<td>K-ras mutations</td>
<td>10–26</td>
<td>0–2</td>
<td>121–123</td>
</tr>
<tr>
<td>Microsatellite instability</td>
<td>15–28</td>
<td>0</td>
<td>122 124–127</td>
</tr>
<tr>
<td>β-Catenin</td>
<td>14–44</td>
<td>0–5</td>
<td>144 147–149</td>
</tr>
<tr>
<td>p53</td>
<td>14–20</td>
<td>53–96</td>
<td>122 131–135</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>10–18</td>
<td>85–95</td>
<td>128–130</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>10–20</td>
<td>80–90</td>
<td>139–141</td>
</tr>
</tbody>
</table>

**Take-home messages**

- Endometrial carcinoma is predominantly a disease of menopause, but it also arises in a setting of oestrogenic milieu. This should not be considered a paradox, since oestrogens are produced not only by the developing ovarian follicle during the reproductive years, but also at menopause from the peripheral conversion (aromatisation) of androgens produced by the adrenal glands and the non-specialised ovarian stroma. Obesity and advanced age are contributory factors. Oestrogen replacement therapy also plays a major role.

- Postmenopausal oestrogen stimulation, when somewhat increased, it is associated with an endometrium which, while atrophic, displays a weak proliferative activity; this is the background upon which endometrial carcinoma most commonly arises.

- Serous papillary and clear cell carcinomas (so-called type II carcinomas) are lethal grade 3 tumours, developing almost exclusively during menopause, but these form only 15% of the total number of tumours. In contrast, the low-grade endometrioid adenocarcinomas, which form nearly 55% of tumours developing in postmenopausal women, have the same favourable prognosis as do the endometrioid adenocarcinomas of similar grade arising in young premenopausal women (so-called type I carcinomas).

- Thus, endometrial carcinoma, as a postmenopausal disease, is not invariably of poor prognosis, as it is generally assumed, and it will be convenient, and indeed necessary, to separate the low-grade/favourable prognosis endometrioid adenocarcinomas from the high-grade/unfavourable prognosis G2 and 3 endometrioid carcinomas and those of the non-endometrioid type.
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In contrast to what it is generally believed, many endometrial carcinomas occurring during the menopause are well-differentiated endometrioid adenocarcinomas having an almost excellent prognosis. The remaining cases are lethal tumours, more or less. Apart from morphology and prognosis, the two groups appear to be different in terms of molecular genetic frequencies. Their taxonomic separation would allow individualisation of treatment.

Competing interests None.

REFERENCES


Review


