Proliferative activity in postmenopausal endometrium: the lurking potential for giving rise to an endometrial adenocarcinoma

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Aims: To investigate proliferation in disease free postmenopausal endometrium and that harbouring endometrial adenocarcinoma—is there a dynamic, yet lurking, potential for atrophic endometrium to give rise to endometrial adenocarcinoma?

Material/methods: The study comprised 84 disease free endometria from asymptomatic postmenopausal women who had undergone hysterectomy for prolapse, and 50 endometrioid cell type endometrial adenocarcinomas with adjacent uninvolved postmenopausal endometrium. The non-neoplastic tissues were separated histologically into active, inactive, and mixed forms, although only the first two categories were studied immunohistochemically for oestrogen and progesterone receptors (ERs, PRs), epidermal growth factor receptor (EGFR), Ki-67, and angiogenic activity.

Results: All postmenopausal endometria were atrophic, but only 42 were inactive; of the remaining samples, 22 were weakly proliferative and 20 were mixed active and inactive. In contrast, the non-neoplastic component of 43 of the 50 endometrial adenocarcinomas examined was of the active form; four specimens were of the pure and 39 of the mixed form. Interestingly, high ER and PR expression was seen in active and inactive endometria, but only the former were EGFR positive and had high proliferative (Ki-67) and angiogenic activity. A similar trend was also shown by the non-neoplastic atrophic endometrium adjacent to endometrial adenocarcinoma.

Conclusions: At least half of the disease free postmenopausal atrophic endometria show a weak proliferative pattern, either diffuse or focal, probably as a response to continuous low level oestrogenic stimulation. These tissues have a latent, although very small, carcinogenic potential, as demonstrated by the immunohistochemical profile and their frequent association with adjacent endometrial adenocarcinoma.

The endometrium, a tissue of continuously changing patterns and immense proliferative activity during a woman's reproductive life, becomes atrophic after the menopause as a result of ovarian failure. At this time there is loss of the functional layer and the endometrial glands take on a simple tubular, often cystic form, showing neither proliferative nor secretory activity, whereas the endometrial stroma turns fibrous.¹

"Excessive and unopposed oestrogenic stimulation is not uncommon after the menopause"

It may appear paradoxical, but it is against this background of atrophy that most endometrial adenocarcinomas develop, and only 15–20% of them arise from a hyperplastic endometrium,² indicating that excessive and unopposed oestrogenic stimulation is not uncommon after the menopause.

There is also a hitherto unspecified proportion of postmenopausal endometria which, despite being atrophic, retain a weak proliferative pattern for many years,^{1–4} probably as a response to continuous low level oestrogenic stimulation. What is the share, if any, of these uterine mucosae in the genesis of endometrial adenocarcinoma? Are these at a higher risk of progression than others or are these only capable, among atrophic endometria, of giving rise to malignant disease?

Our study was designed to explore the above questions, in parallel with examining the frequency of the various

postmenopausal endometrial patterns and their immunohistochemical profile.

MATERIAL AND METHODS

The material used in our study comprised 134 endometrial tissues, of which 84 were collected from asymptomatic postmenopausal women undergoing hysterectomy for a prolapsed uterus, and 50 from patients with endometrial adenocarcinoma, of the well differentiated endometrioid cell type.

The selection criteria for admission into the study were: (1) cessation of menstruation for at least five years; (2) absence of hormonal treatment or irradiation during the menopause; (3) absence of gynaecological symptoms (for the patients without cancer only); and (4) at least three haematoxylin and eosin (H&E) sections available for evaluation of the non-neoplastic endometrium.

Histopathology

The original H&E stained sections were reviewed, and the disease and tumour free postmenopausal endometria were grouped into three categories, namely: (1) atrophic and inactive, (2) atrophic and weakly proliferative, and (3) "mixed" forms.

(1) Atrophic and inactive endometria were defined as those deprived of functionalis and consisting exclusively of a

Abbreviations: EGFR, epidermal growth factor receptor; ER, oestrogen receptor; H&E, haematoxylin and eosin; PR, progesterone receptor

thin basalis with a few narrow tubular glands, lined by cuboidal indeterminate epithelium, showing neither proliferative nor secretory activity. A frequent variant of this structure, tubular atrophy, was an atrophic endometrium with cystically dilated glands, lined by flattened indeterminate type epithelium—cystic atrophy.¹

- (2) Atrophic/weakly proliferative endometria were defined by the following criteria: (a) a shallow endometrium 2.2 mm thick (mean, 2.2; median, 2.0; range, 1.0–3.5), with loss of distinction between the basal and functional layer; (b) proliferative type endometrial glands, somewhat tortuous, with tall columnar pseudostratified epithelium, oval nuclei, and very infrequent mitoses; (c) a dense, fibrotic endometrial stroma, devoid of mitoses.
- (3) The mixed form of endometria was defined as atrophic and inactive endometria showing focal areas of weakly proliferative glands.

The diagnosis of malignant endometrial disease—well differentiated endometrial adenocarcinoma of the endometrioid cell type was reaffirmed, using the 1988 FIGO/ISGP grading system⁵ with the 1995 Zaino's modification.⁶

Immunohistochemistry

Sections were cut at 3 µm and stained immunohistochemically with a standard streptavidin–biotin method for the detection of oestrogen receptor (ER), progesterone receptor (PR), epidermal growth factor receptor (EGFR), and Ki-67, and the alkaline phosphatase–anti-alkaline phosphatase method for endothelial cell staining, as described previously.^{7, 8} For clarity of results, the techniques were applied only on pure histological forms—atrophic/inactive endometria and atrophic/weakly proliferative patterns. Table 1 gives the details of the primary antibodies, the working dilutions, and the antigen retrieval methods used.

Known positive controls were included in each staining run. Omission of the primary antibody and substitution by non-specific immunoglobulin at the same concentration were used as negative controls.

Staining patterns and evaluation

Positivity was indicated as a distinct nuclear reaction for ER, PR, and Ki-67, cytoplasmic staining for EGFR, and membrane staining for endothelial cells.

Assessment of the immunohistochemically stained sections was based on the following guidelines. The percentage of endometrial glandular cells expressing the various antigens under investigation was assessed semiquantitatively. Three different sections for each case were assessed; the counts were performed on the entire endometrial area at ×200 magnification. The mean value was used for statistical analysis.

Angiogenesis was assessed by microvessel counting in the entire endometrial area at ×200 magnification. Three sections were assessed; the final microvessel score was the mean of the vessel counts obtained from these sections. Only blood vessels with a clearly defined lumen or a linear vessel shape, but not single endothelial cells, were taken into account.

In all cases, assessment was performed independently by the two pathologists. Discrepancies were resolved at the conference microscope.

Statistical analysis

Statistical analysis was performed using the GraphPad Prism 3.0 package. The unpaired two tailed *t* test with Welch's correction was applied for testing significant differences between groups of continuous variables. A *p* value < 0.05 was considered significant.

RESULTS

Clinical evaluation

The mean age of the patients in the series was 66.44 (range, 54–84 years), with a mean menopausal duration of 16.0 years (range, 5–34). There was no significant difference between patients having an atrophic and inactive endometrium and those exhibiting an endometrium with atrophy and weak proliferative activity (table 2).

Histological evaluation

The asymptomatic disease free postmenopausal endometria derived from the prolapsed uteruses were atrophic and inactive in 42 of the 84 women, atrophic and weakly proliferative in 22, and of mixed form in 20 women.

The non-neoplastic endometrium adjacent to an endometrial adenocarcinoma was active in 43 of the 50 women; four were in the form of weakly proliferating glands and 39 in the form of a mixed inactive and weakly proliferative endometrium. There were only seven cases lacking endometrial activity.

Immunohistochemical evaluation

Table 3 shows the results of the immunohistochemical evaluation.

Most (> 80%) of the asymptomatic postmenopausal endometria, whether atrophic/weakly proliferative or atrophic/inactive, were ER and PR rich, particularly the epithelial cells. The stain was nuclear, often very strong, exceeding that of the positive control in intensity. However, more than half of the cases showed a partial or complete loss of ovarian hormone receptors from the stromal cells.

EGFR was expressed consistently in all cases of weakly proliferating glands and a large proportion of cells were positive. The same receptor was expressed only in a small number of cases and only in a small proportion of cells in

Table 1 Details of the antibodies, dilutions, and antigen retrieval methods used

Primary antibody	Dilution (incubation time)	Antigen retrieval	Specificity	Source
ID5	1/20 (75 min)	MW	ER	Immunon-Shandon, Pittsburgh, Pennsylvania, USA
IA6	1/20 (75 min)	MW	PR	Immunon-Shandon
H11	1/200 (75 min)	MW	EGFR	Dako, Carpinteria, California, USA
MIB-1	1/75 (75 min)	MW	Ki-67	Dako, Glostrup, Denmark
JC70 (CD31)	1/20 (30 min)	Protease	Endothelium	Dako, Glostrup, Denmark

Incubation with the primary antibodies was at room temperature.

EGFR, endothelial growth factor receptor; ER, oestrogen receptor; MW, microwave heating; PR, progesterone receptor.

Table 2 Clinical characteristics of the patients in the series

Characteristic	Patients with A/I endometrium	Patients with A/WP endometrium	Endometrial cancer patients
Mean (range) age at diagnosis (years)	66.08 (55–84)	66.8 (54–77)	62.5 (51–82)
Mean (range) time at diagnosis after menopause (years)	16.08 (5–34)	17 (5–27)	15.68 (5–37)
Age at menarche (years)	13.1 (11–14)	12.7 (11–14)	12.2 (11–14)
Age at menopause (years)	49.1 (41–51)	49.3 (48–52)	49.9 (46–60)
Time between menarche and menopause (years)	36.1 (29–40)	36.7 (32–42)	37.7 (32–48)
Obesity (mean)	35.7%	45.4%	38%
Nulliparity (mean)	14.2%	13.6%	18%

A/I, atrophic and inactive; A/WP, atrophic and weak proliferative activity.

atrophic/inactive endometria. Expression was cytoplasmic and epithelial cells only were stained.

Similarly, the proliferation rate, assessed by means of the monoclonal antibody MIB-1, was high in weakly proliferating endometria and low (reduced to almost nothing) in atrophic and inactive endometrial tissues.

There was also considerably higher angiogenic activity in the stroma of weakly proliferative endometria compared with that of atrophic and inactive tissues.

Interestingly, the non-neoplastic endometrial glands adjacent to malignant tissues not only showed the histological features of weakly proliferative endometrium but also exhibited an analogous immunohistochemical profile, being ER and PR rich, EGFR positive, and of high proliferative and angiogenic activity (fig 1).

DISCUSSION

The message that emerged from our study is clear and simple: endometrial adenocarcinomas related to endometrial atrophy (as most of these tumours are) originate from weakly proliferating glands, not from a background of endometrial inertia. This is not a paradox, because endometria showing weak proliferative activity are not uncommon after the menopause¹ and, indeed, more than half of the atrophic, disease free, symptom free postmenopausal endometria in our series exhibited such activity, either in a diffuse or focal fashion. Earlier, Archer and colleagues³ and Korhonen *et al.*⁴ investigating endometrial patterns in asymptomatic postmenopausal women, found a similar proliferative activity in approximately 25% of the cases studied and hyperplastic disease in less than 5%, despite using biopsy and curettage specimens rather than hysterectomy samples.

It is probable that the presence of a weak proliferative pattern in a postmenopausal atrophic endometrium is a response of the uterine mucosa to continuous low level oestrogenic stimulation. This is in accord with the reported increased ability of postmenopausal women to convert androstenedione, mainly of adrenal origin, into oestrone in

the adipose tissues of the body using the enzyme aromatase (peripheral aromatisation).^{9–11} The conversion increases with increasing body weight (increased numbers of fat cells) and with advanced age (increased specific activity of aromatase)¹¹; the factors of aging and obesity, both of which are common in patients with endometrial cancer, appear to be additive.¹² Interestingly, oestrone is the most important oestrogen in endometrial carcinogenesis.¹³

However, low level oestrogenic stimulation would be in itself ineffective without the presence of ERs and an operational ER system.^{14–16} An operational ER system is ensured by the immunohistochemical detection of PRs because their synthesis is controlled via a functional ER mechanism.¹⁷ Nonetheless, it is interesting that although all postmenopausal endometria, whether active or inactive, retain their full ER and PR complement, as shown in this and other studies,^{18–19} only those showing a weak proliferative activity were EGFR positive and had a high angiogenic and proliferative (Ki-67) activity. This would account for the growth advantage that the weakly proliferative tissues have among the postmenopausal atrophic endometria. The EGFR is an important mediator of cell proliferation,^{20–22} both in normally cycling^{23–25} and atrophic endometria,²⁶ whereas a high MIB-1 proliferation index is the defining feature of intense proliferative activity.²⁷ Similarly, angiogenesis, as an integral part of endometrial remodelling, is closely associated with increased growth.^{28–29} That weak proliferative activity in the postmenopausal endometrium has a dynamic, yet very low, potential for giving rise to endometrial adenocarcinoma was also inferred by the consistent presence of a focally proliferative pattern in almost all non-neoplastic atrophic endometria adjacent to endometrial adenocarcinomas—an association which, in our material, reached a frequency of 86%. The lack of a visible proliferative pattern in the remaining cases may not necessarily indicate the existence of oestrogen independent endometrial tumours, because foci of proliferative endometrial glands might have been obliterated by the invading tumour.³⁰ However, it should be pointed

Table 3 The immunohistochemical evaluation of the asymptomatic postmenopausal endometria

Parameter	A/I	A/WP	p Value*	Non-neoplastic	p Value†
ER epithelium	85, 22, 90, 20–100	77, 28, 80, 10–100	0.48	75, 31, 80, 10–90	0.56
ER stroma	50, 40, 65, 0–90	39, 30, 0, 0–90	0.18	41, 20, 0, 0–90	0.25
PR epithelium	60, 33, 60, 0–100	76, 19, 80, 40–100	0.22	78, 19, 80, 40–100	0.26
PR stroma	23, 32, 20, 0–90	29, 31, 5, 0–50	0.62	28, 21, 5, 0–50	0.69
EGFR	16, 20, 5, 0–50	77, 17, 80, 30–90	<0.0001	55, 17, 60, 20–90	0.001
MIB1	1, 5, 3, 0–10	11, 5, 10, 2–20	<0.0001	9, 5, 5, 2–15	<0.0001
MVD	14, 8, 10, 4–33	23, 7, 24, 12–36	0.006	27, 6, 26, 14–42	0.001

Values are mean, SD, median, range.

*Note similarities in EGFR, MIB1, and MVD reactivity between cancer tissues and weakly proliferative glands; †p values are given in comparison with atrophic/inactive endometrium.

A/I, atrophic and inactive; A/WP, atrophic and weak proliferative activity; EGFR, endothelial growth factor receptor; ER, oestrogen receptor; MVD, microvessel density; PR, progesterone receptor.

Figure 1 The immunohistochemical profile of weakly proliferative postmenopausal non-neoplastic endometrium found adjacent to endometrioid adenocarcinoma: (A) high oestrogen receptor content, (B) high progesterone receptor content, (C) epidermal growth factor receptor positivity, (D) high Ki-67 proliferation activity, and (E) high microvessel density.

out that the evaluation of proliferative activity in atrophic endometrium should be based on adequate sampling.

Therefore, it is tempting to speculate that all endometrioid adenocarcinomas, whether hyperplasia or atrophy related, are oestrogen dependent and have only varying degrees of hormonal dependence; this being apparently high in the case of hyperplasia (adenocarcinomas of high hormone dependency) and low, and perhaps of longer duration, in endometrial atrophy (adenocarcinomas of low hormone dependency). The risk of progression from simple endometrial hyperplasia to endometrial adenocarcinoma is very low (0.3–1%),^{31–33} and certainly is much lower in the case of

weakly proliferative glands. It is assumed that malignant change against a background of weakly proliferative endometrium may arise from any part of the postmenopausal glands or, indeed, the endometrium, because both endometrium and endometrial glands are involved in their entirety by the proliferative process.

“Although all postmenopausal endometria, whether active or inactive, retain their full oestrogen and progesterone receptor complement, only those showing a weak proliferative activity were epidermal growth factor receptor positive and had a high angiogenic and proliferative activity”

Admittedly, non-cycling proliferative lesions in the endometrium include those with an increased probability of developing into endometrial adenocarcinoma (atypical hyperplasia) and those running a limited risk of such progression (all other forms of endometrial hyperplasia and weakly proliferative endometrium).^{2–34} Endometrioid adenocarcinomas arising through the non-cycling proliferation–neoplasia sequence are oestrogen induced and tend to be well differentiated.^{2–34} This would explain the selective inclusion of G1 endometrioid adenocarcinomas in our series. With regard to G2 and G3 endometrioid adenocarcinomas and the serous papillary and clear cell types, these are high grade tumours,^{35–40} which have a different pathogenetic mechanism and need further investigation.

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Take home messages

- More than half of the asymptomatic postmenopausal women had a weakly proliferative endometrium (either in a diffuse or focal form), featuring an intact oestrogen receptor system, continuous low level oestrogenic stimulation, and a dynamic, albeit extremely low, potential for tumour development
- Well differentiated endometrioid adenocarcinomas related to atrophic endometrium appear to originate from such weakly proliferative type endometrial glands
- The remaining asymptomatic postmenopausal endometria were atrophic and inactive, showing neither proliferative nor secretory activity. This type of endometrium probably has no potential for tumour growth
- It is speculated that endometrial adenocarcinomas of the endometrioid cell type develop only in the presence of oestrogenic stimulation—either excessive, as occurs in a hyperplastic endometrium, or low and perhaps of longer duration, as seen in weakly proliferative glands

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