Factors Predictive of Endometrial Carcinoma in Patients with Atypical Endometrial Hyperplasia on Preoperative Histology

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Abstract. *Aim: To identify predictive factors of endometrial cancer in patients with atypical endometrial hyperplasia (AEH). Patients and Methods: This was a retrospective cohort study of 79 patients diagnosed with AEH. Clinicopathological characteristics of patients and final histology on hysterectomy were reviewed and univariate and multivariate analyses were performed. Results: Nineteen cases of endometrial cancer (24%) were diagnosed at final histology. Most patients had IA (n=15, 79%) grade 1 (n=15, 79%) cancer, but two had FIGO stage IIIC (10.5%). The predictive factors of endometrial cancer on final histology in univariate analysis were: hysteroscopic sampling, older age, post-menopausal status, suspicion of cancer on hysteroscopy and suspicion of cancer at histology. In multivariable analysis, the only predictive factors of endometrial cancer were older age and the suspicion of cancer on hysteroscopy. Conclusion: In patients with AEH on biopsy, our results showed that hysteroscopy could be performed both to assess macroscopic features of malignancy and to orient biopsy.*

Endometrial cancer is the leading gynecological malignancy in Europe and the western countries (1). Endometrioid adenocarcinoma is the most common histology of endometrial cancer, accounting for 75%. Recognized risk factors are genetics (Lynch syndrome and *PTEN* mutation), obesity, tamoxifen treatment, long-term estrogenic stimulation, diabetes and hypertension. Although most endometrial cancer occurs in post-menopausal patients, 5% is diagnosed in younger patients, raising the issue of conservative treatment (2).

Atypical endometrial hyperplasia (AEH) is considered a pre-cancerous lesion. Indeed, a continuum from endometrial hyperplasia without atypia to well-differentiated endometrial carcinoma has been demonstrated (2), and endometrial cancer is detected at final histology in 10-59% of patients with biopsy-diagnosed AEH (3). Two very different situations are faced when a patient is diagnosed with AEH. For menopausal patients, the consensus is to perform a hysterectomy with bilateral salpingo-oophorectomy with a risk of finding endometrial carcinoma at final histology, and hence with a risk of undertreatment and a second operation (4). Antonsen *et al.* reported that lymphadenectomy was appropriate for only 8.75% of patients diagnosed with stage IB or higher endometrial cancer after hysterectomy for AEH (3). On the contrary, AEH may be an indication for conservative management in young patients wishing to preserve their child-bearing potential (5). While most outcomes of conservative treatment of AEH are satisfying, there have been reports of evolution of AEH to invasive endometrial adenocarcinoma with peritoneal spread (5, 6). Hence, clinical and histological criteria are required to assess the possible risk of finding endometrial cancer in patients with AEH on endometrial sampling.

The objective of the present study was to determine the incidence of endometrial carcinoma in patients with AEH and to identify factors predictive of coexisting carcinoma.

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Patients and and Methods

In this retrospective cohort study, all patients diagnosed with AEH on endometrial sampling from January 2002 to January 2012 in Tenon and Bichat tertiary university centers in Paris were included. Institutional Review Board approval was obtained for this study (no. CEROG-2012-GYN-07-02) and all patients gave their informed consent to participate in the study. Patients with evidence of adenocarcinoma in the endometrial sample or without hysterectomy result were excluded from the analysis.

Endometrial sampling could was provided through endometrial biopsy, endometrial curretage or hysteroscopic resection (polypectomy and/or endometrectomy). Explorations for these patients included pelvic examination, transvaginal ultrasonography (TVS) to estimate endometrial thickness and outpatient hysteroscopy. The endometrium was checked for absence of polyps and myoma to ensure the correct measurement of endometrial thickness. For premenopausal patients, endometrial thickness at TVS was considered abnormal when above 10 mm, and for menopausal patients the threshold in patients with and those without hormonal replacement therapy (HRT) was 10 mm and 5 mm, respectively.

Outpatient hysteroscopy was performed using a standard 2.7-mm flexible hysteroscope (Olympus Optical Co, GmbH, Hamburg, Germany). The uterine cavity was distended with normal saline. Illumination was by a high-intensity coldlight source (250 W) through a fiber-optic lead. Images were viewed on a high-resolution color monitor, facing the operator and the patients, using a chip camera. Biopsies were carried out with a Cornier pipelle® (Laboratoire CCD, Paris, France) and the material was fixed in 10% formalin for histology. Hysteroscopic resection was performed through a 10-mm rigid hysteroscope using a monopolar resector in a glycine solution. Criteria for endometrial hyperplasia at hysteroscopy were: focal or extensive, polypoid or papillary mucosal thickening, with or without gland cysts, abnormal vascular network, crowded or abnormally spaced gland openings. Criteria for endometrial cancer at hysteroscopy were: endometrial growth showing a friable consistency with focal necrosis and atypical vessels; endometrial growth could be papillary, polypoid, nodular or mixed type (2).

Criteria used for histological diagnosis were those of the WHO classification of Endometrial Hyperplasia 2003 (7), which includes four categories depending on whether hyperplasia is atypical or not, and whether hyperplasia is simple or complex. The main feature differentiating atypical from non-atypical hyperplasia is the atypical cytology of the glandular lining, as represented by loss of axial polarity, unusual nuclear shapes that are often rounded, irregularity in the nuclear membranes, prominent nucleoli and cleared or dense chromatin. Characteristic features of adenocarcinoma are absent. Discrimination between simple atypical hyperplasia (SAH) and complex atypical hyperplasia (CAH) was not made in a systematic way by the pathology facilities of the study centers, as some authors consider SAH may not even exist or, if it does, it is not of any clinical relevance (8). In this study, the endometrial lesions of atypical hyperplasia are referred to only as AEH.

However, some histological reports concluded the presence of AEH without ruling out carcinoma. We included these patients in our study and registered the histological results as "suspicion of cancer at final histology" for the analysis.

Patients' medical charts were reviewed to determine their clinical and epidemiological characteristics: age, body-mass index (BMI), parity, medical history, history of breast cancer, treatment by tamoxifen, menopausal status, HRT use, hypertension, diabetes and smoking. Data from the endometrial biopsy, preoperative outpatient diagnostic hysteroscopy and TVS were recorded. The way the patients had been managed was also reviewed and analyzed.

We compared patients with final histology of endometrial cancer with those without such a diagnosis. Statistical analysis used the Chi-square test, Wilcoxon test or Fisher's exact test as appropriate. Multivariate analysis included all factors significant in univariate analysis. A p-value of less than 0.05 denotes a significant difference.

Results

Seventy-nine patients were diagnosed with AEH upon endometrial sampling. Fifty-one patients first consulted because of post-menopausal genital bleeding, 18 because of menometrorrhagia, six due to abnormal endometrial thickness on TVS, one because of infertility, one for a cervical polyp, one for pelvic pain and one related to bleeding during tamoxifen treatment for breast cancer. The final diagnosis on hysterectomy was endometrial cancer for 19 patients (24%), AEH for 48 (61%) and lesions less than AEH (*i.e.* hyperplasia without atypia or no hyperplasia) for 12 (15%). Hysterectomy was performed at a median time of 64 days after the diagnosis of AEH.

Mean (SD) age of the patients was 60.1 (11.2) years and 59 (75%) were menopausal (Table I). The mean (SD) parity was 2.0 (1.8) children and the mean (SD) BMI 30.3 (SD=9.5) kg/m^2, with 31 (42%) having a BMI greater than 30 kg/m^2. Among menopausal patients, 23 (39%) had received HRT. Four (5%) had a history of breast cancer and two were treated with tamoxifen. Thirty-eight patients (49%) had hypertension, 15 patients (19%) had diabetes and 10 patients (14%) were smokers. Patients with final diagnosis of cancer were significantly older (66.6 years *versus* 58.0 years, $p<0.001$) and more often menopausal (95% *versus* 68%, $p<0.05$) compared to those without cancer (Table I).

Nineteen patients (24%) had endometrial cancer on hysterectomy analysis (Table II). 15 out of 19 (79%) patients had grade 1 cancer and none had grade 3. The stage according to FIGO 2009 was IA for most patients (79%), IB for two (10.5%) and IIIC for two (10.5%) who had lymph node involvement during initial surgical procedure. Ten patients (53%) had endometrial carcinoma without myometrial invasion.

Nine patients (47%) underwent lymphadenectomy: seven (78%) during the initial surgical procedure and two (22%) during the re-staging surgery. Nine patients underwent pelvic and one para-aortic lymphadenectomy. One patient had positive pelvic lymph nodes and one positive aortic lymph node.

Their mean (SD) follow-up was 32 (30) months. Sixteen patients (84%) were alive and free of disease at follow-up, two patients (10.5%) had local/general relapse and one patient (6%) died from disease (who had presented with initial cancer stage IIIC grade 2).

Table I. *Patients' characteristics according to final histology.*

Characteristic	All patients (n=79)	Patients with endometrial carcinoma (n=19)	Patients without endometrial carcinoma (n=60)	*p*-Value
Mean (SD) age (years)	60.1 (11.2)	66.6 (9.2)	58 (11.1)	0.0031
Menopausal women	59/79 (75%)	18/19 (95%)	41/60 (68%)	0.0313
MHT	23/59 (39%)	9/18 (50%)	14/41 (34%)	0.2648
Obesity	31/73 (42%)	9/19 (47%)	22/54 (41%)	0.7879
Mean (SD) BMI (kg/m^2)	30.3 (9.6)	30.2 (8.0)	30.4 (10.1)	0.2577
Diabetes	15/78 (19%)	2/19 (11%)	13/59 (22%)	0.3360
HBP	38/78 (49%)	8/19 (42%)	20/59 (34%)	0.5867
Breast cancer history	4/78 (5%)	2/19 (11%)	2/59 (3%)	0.2479
Smoker	10/71 (14%)	1/19 (5%)	9/52 (17%)	0.2696

MHT: Menopausal hormone therapy; BMI: body-mass index; HBP: high blood pressure (*i.e.* patients managed for high blood pressure).

Table II. *Characteristics of cancer diagnosed.*

	No.	Percentage
Histological type	19	100.0
Endometrioid	18	95
Endometrioid and papillary	1	5
FIGO stage (2009)	19	100.0
IA*	15	79.0
IB	2	10.5
II	0	0.0
IIIC	2	10.5
Grade	19	100.0
G1	15	79.0
G2	2	10.5
G3	0	0.0
ESMO risk	19	100.0
Low	15	79.0
Moderate	2	10.5
High	2	10.6
Status	19	100.0
Free of disease	16	84.0
Progression	2	10.5
Dead	1	5.0

*Among these 15 patients, 10 had no myometrial invasion. FIGO: International Federation of Gynecology and Obstetrics; ESMO: European Society for Medical Oncology.

Table III. *Presence of endometrial carcinoma on final hysterectomy according to sample mode.*

	Endometrial carcinoma	No endometrial carcinoma	Total
Endometrial biopsy	11 (41%)	16 (59%)	27 (34%)
Operative hysteroscopy	7 (16%)	36 (84%)	43 (54%)
Dilatation and curettage	1 (14%)	6 (86%)	7 (9%)
Cervical polyp	0 (0%)	2 (100%)	2 (2%)
Total	19 (24%)	60 (76%)	79 (100%)

The diagnosis of AEH was made on endometrial sampling obtained by operative hysteroscopy in 43 patients (54%), endometrial biopsy in 27 (34%), endometrial curettage in seven (9%) and cervical polyp in two (3%) (Table III). The rate of cancer found on hysterectomy was 41% (11/27) when AEH was diagnosed on endometrial biopsy, 16% when AEH was diagnosed after operative hysteroscopy (7/43), 14% (1/7) after curettage and 0% (0/2) after removal of a cervical polyp ($p<0.05$). Sixty patients underwent TVS: Forty-three (72%) patients had an abnormal endometrial thickness. There was no difference between patients with or without cancer on hysterectomy.

Sixty patients (76%) had undergone an outpatient diagnostic hysteroscopy or an operative hysteroscopy, 13/19 (68%) in the group of patients with final diagnosis of endometrial cancer and 47/60 (78%) in the group without endometrial cancer. Suspicion of cancer was noted during hysteroscopy in 19 patients (32%) and among them, 10 (53%) had cancer on hysterectomy. Therefore, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of hysteroscopy to assess endometrial cancer were 77%, 81%, 53%, 93% and 80%, respectively. By histology report, there were 14 patients (18%) with histological suspicion of cancer, *i.e.* adenocarcinoma

Table IV. *Factors associated with endometrial cancer.*

	Univariate analysis		Multivariate analysis	
	p-Value	*p*-Value	OR	95% CI
Age	<0.001	0.01	1.012*	1.001-1.023
Post-menopausal status	0.030	0.86	1.025	0.744-1.306
Hormonal replacement therapy	0.146	-	-	-
Hypertension	0.689	-	-	-
Diabetes	0.336	-	-	-
BMI	0.545	-	-	-
Preoperative diagnostic sample obtained without operative hysteroscopy	0.030	0.434	1.148	0.804-1.491
Hysteroscopic suspicion of cancer	0.002	0.007	1.134	1.133-1.551
Histological suspicion of cancer*	0.030	0.227	1.156	0.923-1.389

**i.e.* risk rises by 1.012 fold per years. **When adenocarcinoma could not be ruled-out by the histological report. BMI: Body-mass index; CI: Interval Confidence; OR: Odds Ratio.

could not be ruled-out for these 14 patients. Seven (50%) out of these patients had cancer on final histology.

In univariate analysis, older age, post-menopausal status, the use of blind biopsy rather than the other types of sampling technique for initial diagnosis of HAE, suspicion of cancer on hysteroscopy and suspicion of cancer at histology were determinant factors in diagnosing endometrial cancer on final histology (Table IV). In multivariable analysis, older age and the suspicion of cancer on hysteroscopy were risk factors determinant of endometrial cancer at final histology (Table IV).

Discussion

The present study identifies several risk factors of endometrial carcinoma at final histology in patients with AEH on preoperative endometrial sampling. On univariate analysis, five factors emerged: older age, post-menopausal status, suspicion of cancer on hysteroscopy, suspicion of cancer at histology and the use of blind biopsy rather than the other types of sampling technique for initial diagnosis of HAE. However, on multivariate analysis, the only factors predictive of endometrial cancer were the older age and the suspicion of cancer on hysteroscopy.

In this study, we found that 24% of patients with AEH on biopsy were diagnosed with endometrial cancer at final histology. This rate falls within the range of previous series of AEH (from 10% to 59%) although it is lower than the mean reported value of 42% (3). To understand such a difference, we compared our data to those in the literature. Nine relevant studies were published in the past 10 years, with a number of patients close to or higher than those of our study (1, 3, 8-13). The mean age in our study was 60.6 years, which was older than all these studies, except for the study of Antonsen *et al*. (3). Our rate of menopausal women (75%) was also in accordance with the literature, when reported (3, 8, 11), except for Merisio *et al*. (12) who reported a lower rate of 36%. Thus, neither age nor menopausal status of our population could explain the difference in cancer rate. We show that the rate of endometrial cancer diagnosed after hysterectomy is higher when AEH was diagnosed after blind biopsy rather than the other types of sampling technique. This observation is concordant with other reports (10, 14). Indeed, in most studies reporting rates of cancer of 40%, endometrial biopsy is used more often than in our study: from 45% to 73% (1, 3, 9-12). The only study reporting the lowest rate of endometrial biopsy (19%) is that with the lowest carcinoma rate (10%) (13). This may therefore explain our low cancer rate.

The most striking data of the present study were that the suspicion of cancer on hysteroscopy or at histology was associated with a higher risk of endometrial cancer on hysterectomy. Similarly to Miler *et al*. (15) and Shutter *et al*. (9), we found that "qualifying comments" on pathology reports, which hint at malignancy but do not satisfy histological criteria for such a diagnosis, are associated with a higher rate of endometrial cancer diagnosis at final histology. For Miller *et al*. (15), this rate was 60% *versus* 37.5% if "qualifying comments" were absent, but did not reach statistical significance (p=0.06). Shutter *et al*. reported a 64% cancer rate when such comments were found on pathology reports *versus* 30% without comment ($p<0.05$) (9). We found a rate of 50% *versus* 18% in the absence of suspicion of cancer at histology. Shutter *et al*. suggested the increased cancer rate was the consequence of one of the criteria used to separate AEH and adenocarcinoma: the threshold of 2.1 mm of stromal invasion (9). If that criterion is omitted, it will result in the diagnosis of AEH with a comment that carcinoma cannot be ruled-out, particularly when stromal invasion is seen but is less than 2.1 mm.

Moreover, the devices widely used to perform endometrial biopsies (such as Pipelle de Cornier®) make samples of maximum 2.1 mm, making it more difficult to fulfill the criterion of invasion more than 2.1 mm.

Other factors are, therefore, needed to predict endometrial cancer in patients with the diagnosis of AEH. Although univariate analysis identified epidemiological characteristics of our population such as older age and post-menopausal status as risk factors of endometrial cancer, only older age could predict the presence of endometrial cancer in patients with AEH in multivariable analysis. None of the other classic risk factors, such as hypertension, diabetes and history of breast cancer, were significant in this study. One potential explanation is that patients with AEH share epidemiological characteristics with patients with endometrial cancer. More than one-third of our population was obese and recognized risk factors of endometrial cancer such as hypertension, diabetes and history of breast cancer were observed in 49%, 19% and 5% of our patients, respectively. Another explanation is the small sample size.

Although hysteroscopy emerged as a predictive factor of endometrial cancer, its accuracy was low, raising the issue of the specific macroscopic features of endometrial cancer. Few studies have reported the interest of preoperative diagnostic hysteroscopy. Garuti *et al*. reported very good values for sensitivity, specificity, NPV and PPV values of hysteroscopy for predicting the presence of endometrial adenocarcinoma (84.6%, 100%, 87.5% and 100%, respectively) in patients with AEH diagnosed at histology on biopsy (16). Among 25 patients with AEH on biopsy, the authors reported that all nine with suspicion of malignancy on hysteroscopy had endometrial carcinoma on hysterectomy. Of the remaining 16 patients with no suspicion of malignancy, only two (12.5%) had endometrial carcinoma at final histology (16). In another retrospective study of 17 patients diagnosed with AEH and normal hysteroscopy, Agostini *et al*. reported only one case (5.9%) of endometrial adenocarcinoma on hysterectomy (17) . The NPV was therefore high (94%) for this small series. Finally, despite the limits of diagnostic hysteroscopy, all these data associated with our results suggest its use in cases of AEH to better describe the lesion and to allow oriented biopsies. In addition, hysteroscopy is also a major criterion to opt for conservative treatment. After a first hysteroscopic resection of the endometrial lesion followed by hormonal therapy, hysteroscopy remains the only tool for assessing therapeutic response adequately (5).

Another issue is to avoid under- or overtreatment of patients with AEH with factor risks of endometrial cancer. In our study, 79% of patients had stage IA (20% without myometrial invasion) and 79% of patients grade 1 endometrial carcinoma, suggesting that the vast majority of patients had no benefit from pelvic lymphadenectomy (18, 19). Our results are in agreement with those of previous studies (1, 3, 10). However, four out of 19 women were of intermediate- or high-risk groups, suggesting that for patients with a risk of endometrial cancer on diagnostic hysteroscopy, preoperative magnetic resonance imaging could be discussed to assess myometrial invasion in deciding to opt for pelvic lymphadenectomy or sentinel node biopsy (20). Only Antonsen *et al*. reported the surgical management of such women, with a low rate of lymphadenectomy (8.75%) for women with FIGO stage greater then IA (3).

Some limits of the present study have to be underlined. Firstly, its retrospective nature cannot exclude bias. Indeed, hysteroscopic data were available for only 76% of patients. However, our series remains the largest evaluating the contribution of diagnostic hysteroscopy. Another possible cause of bias is the heterogeneous management of patients diagnosed with AEH since the study took place in two different centers over 10 years. Finally, although our results support the contribution of diagnostic hysteroscopy, an international consensus on hysteroscopic criteria to differentiate AEH from endometrial carcinoma is required.

In conclusion, our results confirm that hysteroscopy can be recommended both to assess macroscopic features of malignancy and to allow oriented biopsy to better identify among patients with AEH those with a risk of endometrial cancer.

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