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CLINICAL ARTICLE

Gynecology

Risk assessment for endometrial cancer in women with abnormal vaginal bleeding: Results from the prospective IETA-1 cohort study

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Abstract

Objective: To investigate the association between personal history, anthropometric features and lifestyle characteristics and endometrial malignancy in women with abnormal vaginal bleeding.

Methods: Prospective observational cohort assessed by descriptive and multivariable logistic regression analyses. Three features—age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), and nulliparity—were defined a priori for baseline risk assessment of endometrial malignancy. The following

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variables were tested for added value: intrauterine contraceptive device, bleeding pattern, age at menopause, coexisting diabetes/hypertension, physical exercise, fat distribution, bra size, waist circumference, smoking/drinking habits, family history, use of hormonal/anticoagulant therapy, and sonographic endometrial thickness. We calculated adjusted odds ratio, optimism-corrected area under the receiver operating characteristic curve (AUC), R^2, and Akaike's information criterion.

Results: Of 2417 women, 155 (6%) had endometrial malignancy or endometrial intraepithelial neoplasia. In women with endometrial cancer median age was 67 years (interquartile range [IQR] 56–75 years), median parity was 2 (IQR 0–10), and median BMI was 28 (IQR 25–32). Age, BMI, and parity produced an AUC of 0.82. Other variables marginally affected the AUC, adding endometrial thickness substantially increased the AUC in postmenopausal women.

Conclusion: Age, parity, and BMI help in the assessment of endometrial cancer risk in women with abnormal uterine bleeding. Other patient information adds little, whereas sonographic endometrial thickness substantially improves assessment.

KEYWORDS
endometrial neoplasms, endometrium, uterine hemorrhage

1 | INTRODUCTION

Endometrial cancer (EC) is the second most common gynecologic malignancy, with 382 000 new cases annually worldwide, and is the third cause of death from women's cancers in industrialized countries.[1] Its incidence is steadily increasing and is projected to do so even more in the following decades.[2]

Abnormal vaginal bleeding is the presenting complaint in up to 90% of women with EC.[3] However, most women with abnormal vaginal bleeding do not have EC, but experience blood loss due to various benign pathologies.[3,4]

Physicians working in an ambulatory care setting are often the first to evaluate women with abnormal bleeding. A detailed patient history is generally assumed to provide a good estimate of a patient's cancer risk and subsequent need for referral to secondary care. The extent to which these baseline factors could support triage for further diagnostic testing remains unclear. Further testing often consists of transvaginal ultrasound including measurement of the endometrial thickness[5,6] and/or endometrial sampling.[7]

In this study we aim to explore which personal history, anthropometric, or lifestyle characteristics are helpful when assessing the risk of cancer in women presenting with abnormal vaginal bleeding.

2 | MATERIALS AND METHODS

This diagnostic cohort study is part of the International Endometrial Tumor analysis (IETA) -1 prospective observational multicenter study, which consecutively recruited premenopausal and postmenopausal women presenting with abnormal vaginal bleeding for transvaginal ultrasound examination between January 1, 2012 and December 31, 2015. This took place in 12 centers specialized in gynecologic ultrasound in nine European countries, including secondary and tertiary centers specialized in gynecologic ultrasound. The study was approved by the Leuven ethics committee EC Research (S52897/ML7087) on April 19, 2010 and by the ethics committees of all participating centers.

The inclusion criterion was abnormal, not pregnancy-related, uterine bleeding (i.e., postmenopausal bleeding, heavy menstrual bleeding, intermenstrual bleeding, bleeding during continuous combined estrogen-gestagen therapy, or abnormal bleeding during sequential estrogen-gestagen therapy). Exclusion criteria were failure to perform ultrasound examination, no initial endometrial thickness measurement result, missing histology combined with follow up of less than 1 year, pregnancy-related bleeding, or bleeding not originating in the uterus, e.g., vaginal or cervical cancer.

All patients gave informed consent. Transvaginal unenhanced ultrasonography was performed using the IETA examination technique.[8] The endometrial thickness is measured in the sagittal plane including both endometrial layers. When the endometrium could not be seen clearly in its entirety, it was reported as “non-measurable” and no attempt was made to measure it. Endometrial sampling was performed following the ultrasound scan. The histologic end points were endometrial atrophy, proliferative or secretory endometrium, endometrial hyperplasia without atypia, endometrial polyp, intracavitary leiomyoma, endometrial intraepithelial neoplasia, EC, and miscellaneous (e.g., endometritis). For each patient a single outcome was recorded. In the presence of multiple pathologic outcomes, a

single outcome was allocated to each woman using the following hierarchy: EC, endometrial intraepithelial neoplasia, polyp, leiomyoma, hyperplasia without atypia. For patients without final histology, follow up of at least 1 year was used as proxy for the absence of malignancy at inclusion.

For a subset of postmenopausal women with abnormal bleeding, additional clinical variables were collected: information on lifestyle (smoking, alcohol consumption, and physical exercise) and body constitution (lean, abdominal adiposity, female adiposity, bra cup size, waist circumference). Body constitution was noted as perceived by the recruiting physician. Waist circumference was measured. Both patient-reported and physician-ascertained height and weight were allowed for inclusion in this study. The results were recorded in a specially designed web-based database.

Multivariable analyses were performed to assess the relationship between clinical risk factors and the composite outcome of endometrial malignancy, consisting of EC and/or endometrial intraepithelial neoplasia. Risk factors for endometrial malignancy

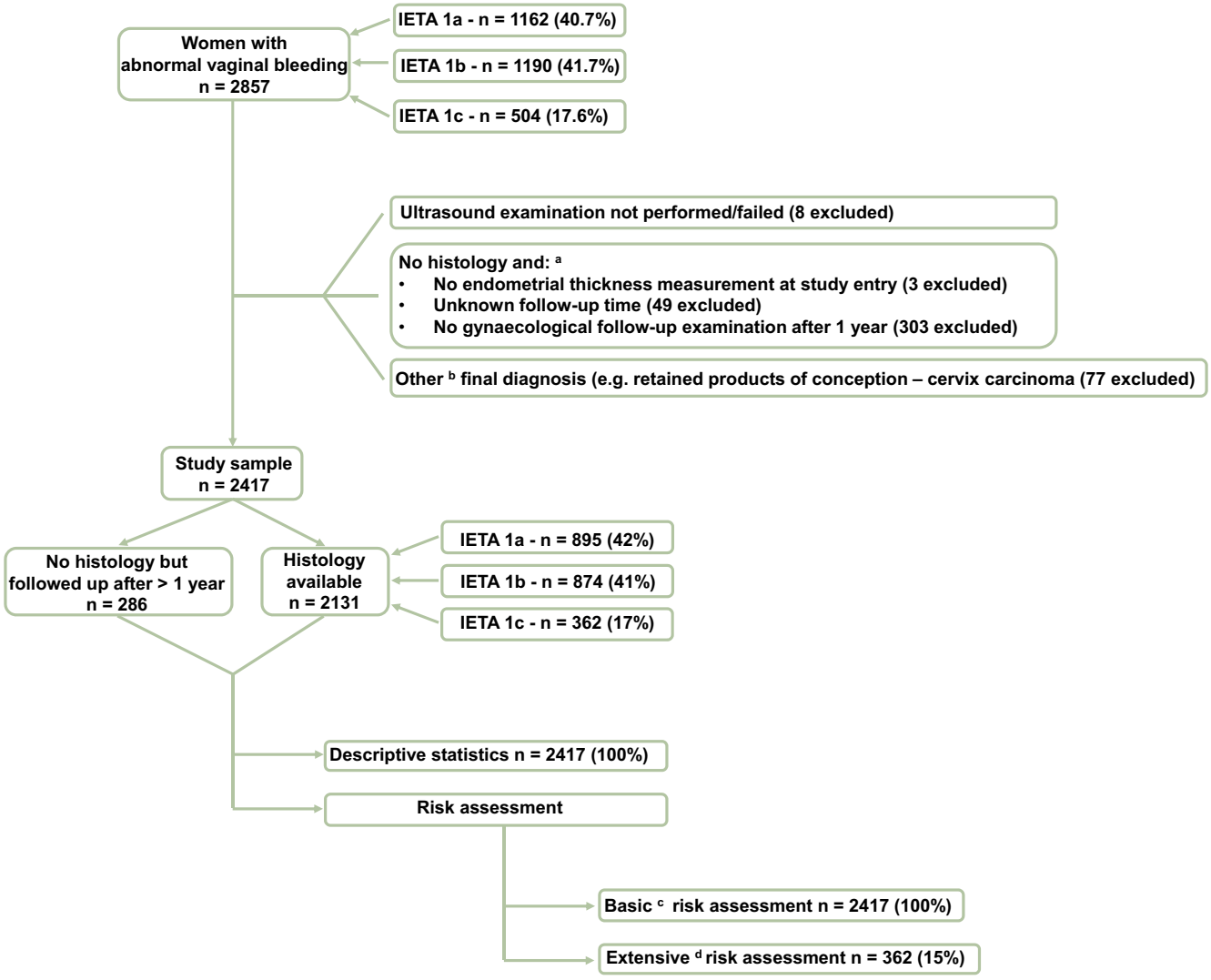

FIGURE 1 Flowchart of inclusions/exclusions. [a]The 355 (3 + 49 + 303) patients excluded because of missing histology and missing endometrial thickness or lack of follow-up, were slightly younger, had slightly thinner endometria, and less frequently visible lesions at sonohysterogram than the patients included in the analysis. Their median age was 47 years (interquartile range [IQR] 40–55 years), the median endometrial thickness (ET) was 8.1 mm (IQR 5.0–9.4 mm), and the percentage with a lesion seen at sonohysterogram was 13%. For comparison, in 2417 included patients, the median age was 50 years (IQR 43–57 years), median ET was 8.8 mm (IQR 5.2–10.0 mm), and the percentage with a lesion seen at sonohysterogram was 33%. [b]Other than the histologic outcomes considered for inclusion (i.e., other than endometrial atrophy, endometrial polyp, intracavitary myoma, endometrial cancer, endometrial intraepithelial neoplasia, proliferative or secretory endometrial changes, endometritis or endometrial hyperplasia without atypia). [c]Main risk assessment based on age, body mass index, and number of deliveries with the following added one at a time: Age at menopause, use of hormonal therapy, use of intrauterine contraceptive device, use of anticoagulant therapy, and sonographic endometrial thickness. [d]Subgroup risk assessment based on age, body mass index, and number of deliveries with the following added one at a time: Smoking, alcohol consumption, physical exercise, use of anticoagulant therapy, family history of endometrial cancer, diabetes, hypertension, age at menopause, waist circumference, bra cup size, body fat distribution, and hormonal therapy

were defined upfront through iterative expert discussion. We use the term risk factor to indicate factors with a potential diagnostic value, but this does not imply that these factors cause cancer. Baseline risk assessment entailed the construction of a multivariable logistic regression model based on three factors: age, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters), and nulliparity. These three clinical variables are easy-to-assess baseline characteristics and their clinical relevance is supported by the literature.[9] Information pertaining this triad, as well as age at menopause, use of hormonal or anticoagulant therapy, and use of an intrauterine contraceptive device had to be collected in all women and were added one by one to the baseline triad. In a subgroup of postmenopausal women with abnormal uterine bleeding, the additionally added variables were: presence of diabetes or hypertension, physical exercise, waist circumference, bra cup size, smoking habits, alcohol consumption, and family history of cancer. Apart from these clinical factors, sonographic endometrial thickness measurement was also examined when added to the baseline risk assessment.

Only complete cases, i.e., individuals with observed values on both the studied risk factor and the histologic outcome(s), were included.

We started with descriptively assessing the presence of baseline risk factors, for each individual histologic end point. All subgroup analyses (premenopausal vs. postmenopausal) were exploratory and specified a posteriori.

Test statistics were calculated in those cases providing information on all risk factors, by calculating the odds ratio (OR) for the outcome of malignant versus benign pathology of each risk factor, adjusted for age, BMI and parity, the resulting optimism-corrected area under the receiver operating characteristic curve (AUC), the Nagelkerke R^2, and Akaike's Information Criterion. Higher values for AUC and R^2 signify better discrimination; whereas better fit of the model is reflected by lower values of Akaike's Information Criterion. Test statistics were calculated for all patients regardless of menopausal status, as well as for premenbopausal and postmenopausal women separately. Postmenopause was defined as absence of vaginal bleeding for at least 1 year after the age of 40 years, provided that amenorrhea was not explained by pregnancy, medication, or disease.

All statistical analyses were performed using R 4.0.1, (https://www.r-project.org/; R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

The database consisted of 2856 consecutive women presenting with abnormal vaginal bleeding. Of these, 439 were excluded: eight patients had no ultrasound data, 77 had pathologies also causing bleeding other than those specified (see Materials and methods section) in the inclusion criteria (retained products of conception or cervical cancer), and 354 women had no histologic diagnosis combined with no follow up after more than 1 year or no endometrial thickness measurement at study entry (Figure 1).

The study sample used for analysis consisted of 2417 women, of whom 2131 (88.2%) had a final histologic diagnosis. In 286 women (11.8%), the histology was unknown, but a tentative diagnosis of benign histology was made based on absence of malignancy after more than 1 year of follow up (Figure 1).

In a subset of postmenopausal women with abnormal bleeding (362/2417; 15.0%), lifestyle (smoking, drinking, and exercise habits) and constitution (bra cup size, fat distribution, waist circumference) variables were recorded.

Histology was obtained by office endometrial sampling in 762/2417 (31.5%) women, dilatation and curettage in 61/2417 (2.5%), directed or random biopsies during hysteroscopy in 1055/2417 (43.6%) and after hysterectomy in 253/2417 (10.5%). According to histology, atrophy was found in 224/2417 (9.3%) women, a focal intracavitary lesion (polyp or myoma) in 972/2417 (40.2%), malignancy or endometrial intraepithelial neoplasia in 155/2417 (6.4%), hyperplasia without atypia in 148/2417 (6.1%), and endometritis, and proliferative or secretory changes in 632/2417 (26.1%) (Table 1).

Detailed information on timing, duration, and intensity of bleeding was available for 1236/2417 (51.1%) patients (Tables S1 and S2). The majority (743/1236, 60.1%) presented with non-cyclical bleeding only, whereas 23% (284/1236) had cyclical bleeding and 16.9% (209/1236) combined cyclical and non-cyclical bleeding (Table S2). Malignancy/endometrial intraepithelial neoplasia was found in 11.4% (85/743), 2.8% (8/284), and 1.9% (4/209) of women presenting with non-cyclical, cyclical, and combined cyclical and non-cyclical bleeding,

TABLE 1 Demographic background data and outcomes ($n = 2417$)[a]

Age, years	**50 (43–57)**
Body mass index[b]	25 (22–29)
Parity	2 (0–10)
Postmenopausal	1002 (41%)
Histologically confirmed diagnosis	
Atrophy	224 (9%)
Endometrial polyp	749 (31%)
Intracavitary myoma	223 (9%)
Malignancy	137 (6%)
Endometrial intraepithelial neoplasia	18 (1%)
Proliferative changes	304 (13%)
Secretory changes	306 (13%)
Hyperplasia without atypia	148 (6%)
Endometritis	22 (1%)
No histology but followed up after >1 year	286 (12%)
Unenhanced ultrasound characteristics	
Visible endometrium	2178 (90%)
Endometrial thickness (mm)	9.0 (6.0–13.3)

[a]Results are presented as median (interquartile range) or number (percentage).

[b]Body mass index calculated as weight in kilograms divided by the square of height in meters.

TABLE 2 The association between risk factors and endometrial cancer and/or endometrial intraepithelial neoplasia in all patients: Multivariable analyses based on $n = 2417$

Variable	Unit	OR[a]	95% confidence interval		AUC optimism corrected	R^2 optimism corrected	AIC
Baseline variables							
Age	Per 5 years	1.56	1.46	1.67	0.82	21%	947.8
Body mass index[b]	Per 5 kg/m^2	1.13	0.98	1.30			
Nulliparity	No versus Yes	0.78	0.48	1.29			
Added value of non-sonographic characteristics (over baseline variables) (each statistic represents the performance of combination of the respective variable and the three baseline variables)							
Hormonal therapy	Yes versus No	0.42	0.25	0.69	0.83	22%	936.4
Intrauterine contraceptive device present	Yes versus No	0.44	0.06	3.25	0.82	20%	949.0
Anticoagulant therapy	Yes versus No	0.71	0.43	1.20	0.82	21%	948.2
Age at menopause	Per 5 years	1.11	0.87	1.41	0.82	21%	949.1
Added value of endometrial thickness on ultrasound (over baseline variables) (each statistic represents the performance of combination of the respective variable and the three baseline variables)							
Endometrial thickness	Per 5 mm	1.94	1.71	2.20	0.86	33%	820.1
Endometrial thickness unmeasurable	Yes versus No	4.86	2.70	8.76			

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; OR, odds ratio.

[a]All odds ratios are adjusted for age, body mass index, and parity; baseline characteristics are those for which there is strong evidence in the literature.[9]

[b]Body mass index calculated as weight in kilograms divided by the square of height in meters.

respectively. When all bleeding types were graded and analyzed together, we found that malignancy/endometrial intraepithelial neoplasia presented with slight blood loss or spotting in 60.4% (61/101), compared with 40.2% (540/1344) in benign outcomes. Blood loss was moderate in 20.8% (21/101) and heavy-to-extreme in 18.8% (19/101) in malignancy/endometrial intraepithelial neoplasia, versus 18.2% (245/1344) and 41.6% (559/1344), respectively, for benign outcomes.

Information on age, menopausal status, age at menopause, parity, BMI, hormonal and anticoagulant therapy, and use of intrauterine contraceptive device was available for all 2417 women (Table S3). Information pertaining to past medical history or family history of cancer was available for 1236/2417 (51.1%) (Table S3).

Summary statistics for the 2131 patients with available histology are depicted in Table 1, and Tables S2 and S3. Of the 2417 women included, the median (range) age was 50 years (19–94 years) and median parity was 2 (0–10). Their median (range) height and weight were 164 cm (143–188 cm) and 68 kg (40–180 kg), respectively. Of all 2417 women included, 1415 were premenopausal (59%) and 1002 were postmenopausal (41%).

Over one-quarter of all patients (663/2417; 27%) used hormonal therapy. The median age of women with endometrial malignancy was 67 years (IQR 56–75 years) versus 49 years (IQR 43–55 years) for those with benign outcomes. The median BMI of women with endometrial malignancy was 26 (IQR 24–31) versus 25 (22–29) for their benign counterparts. Fourteen percent of women with cancer were nulliparous, as opposed to 21% of women with benign outcomes.

Combining age, BMI, and parity into a "baseline risk assessment" for all patients ($n = 2417$), by means of multivariable logistic regression, generated an AUC of 0.82 (Table 2). Adding hormonal therapy to the baseline model increased the AUC very little (0.83). None of the other variables, when added to the baseline model one by one, resulted in an increased AUC compared with the baseline. This was the case for the models of both premenopausal and postmenopausal women (Table 2, and Tables S4 and S5). Adding sonographic endometrial thickness to the baseline model resulted in an increased AUC in postmenopausal women (from 0.73 to 0.85) but not in premenopausal women (from 0.67 to 0.66) (Tables S4 and S5).

Most women with endometrial malignancy were postmenopausal (83%), had never smoked (63%), reported a moderate alcohol consumption below 7 units per week (57%), no or limited physical exercise (43% and 30%, respectively) and did not take anticoagulant therapy (82%). Of women with endometrial malignancy, 20% had diabetes and 12% used hormonal therapy, as opposed to 6% and 28% of women with benign outcomes (Table S3).

In the group of 362 consecutive postmenopausal women, knowledge of diabetes, bra size, and use of hormonal therapy ameliorated risk assessment; adding other non-sonographic factors hardly changed the AUC (Table 3).

4 | DISCUSSION

Our study shows that knowledge about age, BMI, and parity is informative in assessing the risk of endometrial malignancy in women with abnormal uterine bleeding. Adding other non-sonographic patient information assumed to be associated with increased risk of

TABLE 3 The association between risk factors and endometrial cancer and/or endometrial intraepithelial neoplasia in subgroup of postmenopausal women only with additional clinical information: Multivariable analyses based on data from $n = 362$)

Variable	Unit	OR[a]	95% confidence interval		AUC optimism corrected	R^2 optimism corrected	AIC
Baseline variables							
Age	Per 5 years	1.54	1.32	1.80	0.76	16%	268.6
Body mass index[b]	Per 5 kg/m^2	1.33	1.07	1.65			
Nulliparity	No versus Yes	0.65[e]	0.26	1.63			
Added value of non-sonographic characteristics (over baseline variables) (Each statistic represents the performance of combination of the respective variable and the 3 baseline variables)							
Smoking	Past smoker versus no smoker	0.41	0.83	1.66	0.75	15%	271.3
	Current smoker versus no smoker	0.56	1.66	4.95			
Increasing alcohol consumption	Ordinal[c]	0.98	0.64	1.50	0.75	15%	270.6
Increasing physical exercise	Ordinal[c]	0.96	0.71	1.29	0.75	15%	270.5
Anticoagulant therapy	Yes versus No	0.65	0.29	1.47	0.75	15%	269.5
Family history of endometrial cancer	Yes versus No	1.05	0.28	3.94	0.75	15%	270.6
Diabetes	Yes versus No	2.38	1.07	5.34	0.76	16%	266.4
Hypertension	Yes versus No	1.38	0.70	2.72	0.75	15%	269.7
Age at menopause	Per 5 years	0.94	0.66	1.34	0.75	15%	270.5
Waist circumference	Per 10 cm	0.99	0.71	1.39	0.75	15%	270.6
Increasing bra cup size	Ordinal[c]	1.33	0.99	1.77	0.76	16%	270.0
Constitution	Female adiposity versus abdominal adiposity	1.00	0.45	2.20	0.75	15%	271.4
	Lean versus abdominal adiposity	0.61	0.24	1.57			
Hormonal therapy[d]	Yes versus No	0.36	0.15	0.90	0.77	17%	264.8

Abbreviations: AIC, Akaike information criterion; AUC, area under the curve; OR, odds ratio.

[a]All odds ratios are adjusted for age, body mass index, and parity; baseline characteristics are those for which there is strong evidence in the literature.[9]

[b]Body mass index calculated as weight in kilograms divided by the square of height in meters.

[c]Levels are specified in Table S1; for each variable the lowest level of exposure was used as comparator.

[d]Any hormonal therapy, including sex steroid hormones as well as selective estrogen receptor modulators and aromatase inhibitors.

[e]The OR of 0.65 should indicate that, in this subgroup of postmenopausal women with additional clinical information (n = 362), nulliparity is a risk factor for endometrial cancer and/or endometrial intraepithelial neoplasia, whereas giving birth to one or more children has a protective effect against endometrial cancer and/or endometrial intraepithelial neoplasia.

malignancy did not allow for better risk assessment. Conversely, adding the sonographic endometrial thickness measurement strongly improved the discrimination between benign and malignant endometrial outcomes.

The strengths of the present study are its prospective design, the large numbers of patients included, the international contribution of cases, and the use of uniform, web-based data-capturing sheets. Bleeding pattern has once again been demonstrated to have a more complex correlation with endometrial pathology than commonly considered. Our data suggest focusing more on bleeding frequency than on its intensity/duration. As opposed to the textbook enumeration of risk factors, we propose a triad of factors, comprising easily assessed clinically relevant information. These might save time and energy for healthcare professionals working in a first-line setting. Our study demonstrates, contrary to the common knowledge, several risk factors that give hardly any added value in the diagnosis of endometrial cancer. We feature a possible novel factor (bra cup size) in endometrial cancer assessment. We provide globally relevant information for first-line management worldwide, including those countries with more limited availability of more technical tests such as ultrasound scan or magnetic resonance imaging. Of 2856 patients recruited to the study, 22% had no histologic diagnosis and, to avoid selection bias, "no sign of malignancy after 1 year of follow up" was used as proxy for benign outcome.

We acknowledge the limitation of the lower numbers in the subgroup of 362 postmenopausal women with more detailed information. However, we found this information sufficiently illustrative to present as a secondary end point. Although part of the data is not robust enough to draw definitive conclusions, we think this might support other clinical researchers to design future studies on the subject. We acknowledge the possibility of recall bias when

quantifying past and present medication use and lifestyle habits, as well as reporting on family history of cancer. We accounted for this by limiting family assessment to first-degree relatives.[10] We are also aware of the difficulty for patients to give precise information on bleeding pattern as well as of recruiting physicians' appraisal of body fat distribution. We attempted to reduce this variability by using uniform terminology. Risk factors, such as late menopause or high BMI, hinge on the paradigm of estrogens as driver of EC.[9,11–14] A higher BMI is associated with increased androgen aromatization to estrogen in adipocytes, lower serum levels of progesterone and sex-hormone-binding globulin, and possibly adiposity-related cytokines. We found that use of hormone therapy was associated with a decreased risk. This is in line with previous studies[15,16] and is probably attributable to the stabilizing effect of progesterone on the endometrium or to the fact that hormonal therapy in itself may cause bleeding. Our data do not confirm independent associations between EC and increasing waist circumference; we did not further investigate the effects of waist-to-hip ratio, waist-to-height ratio, or height.[9,13,17] Previous research reported bra size to be associated with increased breast cancer mortality,[18] but our study found a weak association between increasing bra cup size and EC. We hypothesize that both mammary and endometrial glands reflect circulating estrogen concentrations. The published protective effect of increasing parity[19] may be a result of high progesterone levels during pregnancy, the hypoestrogenic state during breast feeding, or, possibly, to the clearing of (pre)malignant endometrial cells after childbirth. Our data on bleeding pattern is in line with Ewies and Musonda[11] showing that bleeding amount is less important than frequency for determining cancer risks. We could not confirm the added value of lifestyle habits on cancer risk. Physical activity[9,12,20] and smoking have been reported to have a protective effect.[9,12,21] Alcohol has been shown to have a J-shaped association with EC risk,[22] moderate use reducing the risk, while abuse increased cancer risk. Our results show that even though hypertension was more common among women with EC than in any other histologic outcome group, adding it to the baseline triad did not improve risk assessment for EC.[9,17,23] We found a decreased cancer risk ensuing anticoagulant therapy. Anticoagulant use in itself is a likely competing reason for abnormal blood loss. Other studies have shown that the risk of EC increases with each additional relative affected with endometrial cancer and that risks increase the younger and more closely related these relatives are.[24]

Our results highlight that patients' age, parity, and BMI are clinical predictors of endometrial cancer risk in women with abnormal vaginal bleeding, and that other non-sonographic factors do not add much to risk assessment in these women. Our study confirms the value of sonographic endometrial thickness measurement in postmenopausal women with abnormal uterine bleeding. In premenopausal women, the measurement of endometrial thickness is of less added value. For these women, other features such as gray-scale ultrasound morphology and Doppler patterns[25] may be more discriminative. In our study the IQR for age was 43–57 years. This probably reflects the higher incidence of abnormal uterine bleeding in the perimenopausal age group. The diagnosis of the menopausal status in this age group is often tentative: e.g., a regular menstrual cycle may resume after a period of amenorrhea of more than 12 months or frequent episodes of uterine bleeding may occur in the absence of significant ovarian activity mimicking a menstrual cycle. In contrast to menopausal status, the use of age as a risk factor is not prone to interpretation and has to be preferred.

Our study has shown that patient characteristics other than age, parity, and BMI are of little added value to assess the risk of EC in women with abnormal uterine bleeding. In abnormal uterine bleeding, knowledge about patient's age, parity, and BMI is sufficient as basic risk assessment for endometrial malignancy in women with abnormal bleeding, before referral for additional tests, such as sonographic endometrial thickness measurement. In postmenopausal women, sonographic measurement of endometrial thickness substantially improves EC risk assessment.

AUTHOR CONTRIBUTIONS

JYV and LW performed the statistical analyses. JYV, RH, and TVdB interpreted the data; they created an initial draft of the article, which all other authors critically appraised. TVdB, EE, DT, and TB elaborated the study design. TVdB, MAP, FPGL, PS, LJ, CVP, and RF recruited all patients, took the detailed patient history, performed the medical examinations, i.e. respectively collected and estimated all objective and subjective clinical variables, and entered all patient data in the online repository. All authors gave their approval for the final version of this paper to be published.

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CONFLICTS OF INTERESTS

None declared. Completed disclosure of interest forms are available to view online as supporting information.

DATA AVAILABILITY STATEMENT

No. Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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