Vabrasio is a reliable test to rule out endometrial cancer

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ABSTRACT

INTRODUCTION: Endometrial cancer is the most common gynaecological cancer in Denmark, and its incidence peaks in the postmenopausal years. The aim of the present study was to evaluate the effectiveness of vacuum aspirator (vabrasio) for the detection of endometrial cancer in terms of sensitivity, specificity and predictive value.

METHODS: A cohort counting 503 women who had vabrasio was evaluated retrospectively. The women included were consecutive patients who had received vabrasio at the Department of Gynaecology and Obstetrics at Herning Hospital, Denmark, during a two-year period. They were identified by searching the hospital database for the International Classification of Diseases, tenth version (ICD-10) code for vabrasio.

RESULTS: The indications for vabrasio were postmenopausal bleeding (45%), meno/metrorrhagia (43%) and thickened endometrium/polyp (6%). The first evaluation by vabrasio was normal in 381 women (76%), insufficient in 83 women (17%), 22 (4%) had endometrial cancer and 17 (3%) had another non-malignant diagnosis. The first evaluation for cancer with vabrasio had a sensitivity of 81%, a specificity of 100% and predictive values of 100% (positive) and 99% (negative).

CONCLUSIONS: Vabrasio has a good diagnostic reliability with respect to endometrial cancer, but has some shortcomings due to insufficient sampling for diagnosis.

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Endometrial cancer is the most common gynaecological cancer, and the maximum incidence of the condition is seen in postmenopausal years. It is the fifth most common cancer in Danish women [1]. The most common type of endometrial carcinoma is the endometrioid adenocarcinoma, which develops from hyperplasia of the endometrium, particularly when exposed to an excess of oestrogen [2, 3]. The premalignant hyperplasia, i.e. atypical endometrial hyperplasia, displays similar cellular and structural changes as true cancer, but does not show invasion into the connective tissues.

Risk factors for endometrial cancer were related to reproduction such as nulliparity, late age at menopause and early age at menarche. Other risk factors are more directly related to female hormone levels, e.g. polycystic ovary syndrome, diabetes, hypertension and obesity. However, smoking, low-fat diets and exercise decrease the incidence of endometrial cancer, probably owing to an indirect influence on the oestrogen levels and the stimulation on the endometrial epithelium [4].

The diagnosis of endometrial cancer is usually made by endometrial sampling. In Denmark, a device called the vacuum aspirator (vabrasio) is used for histopathology assessment. Other methods include direct biopsy of endometrial cells as a minimally invasive alternative and the classic sampling by dilatation and curettage (D&C) [5]. Various levels of effectiveness in the detection of cancer were reported [3, 6].

The aim of this study was to assess the value of vabrasio in the context of a quality assurance project on detection of endometrial cancer following clinical observation of a number of insufficient samples from the vabrasio technique. We undertook the study after our department was approached to consider new types of endometrial sampling.

METHODS

We retrospectively reviewed 503 women who had an initial diagnostic vabrasio before planning and executing other gynaecological procedures besides ultrasound. The women studied were consecutive patients at the Gynaecology Department at Herning Hospital, Denmark, during the two-year period 2012-2013. The electronic medical records were scrutinised after having been identified using the ICD-10 classification searching for vabrasio (LCA10A) in the hospital database. The data registered were indications for endometrial biopsy, histopathology findings, co-morbidity such as hypertension, diabetes, other medical conditions, reproduction data, age at menopause, parity and consumption of tobacco and alcohol.

! ABBREVIATIONS

BMI = body mass index
D&C = dilation and curettage
HNPCC = hereditary non-polyposis colon cancer
SD = standard deviation

ORIGINAL ARTICLE

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TABLE 1

Clinical data of the 503 women who had an initial diagnostic vabrasio.

Age, yrs, mean (± SD)	56 (± 25,95)
Age at menopause, yrs, mean (± SD)[a]	51 (± 29,63)
BMI, kg/m², mean (± SD)	28 (± 15,58)
Body weight, kg, mean (± SD)	78 (± 40,172)
Parity, mean (± SD)	2.5 (± 0,7)
Hypertension, n (%)	130 (26)
Type 2 diabetes, n (%)	33 (7)
Hypothyroidism, n (%)	15 (3)
Previous breast cancer, n (%)	18 (4)

BMI = body mass index; SD = standard deviation.
a) n = 191.

TABLE 2

Indications for the initial diagnostic vabrasio in 503 women.

Indication	n (%)
Postemenopasual metrorrhagia	227 (45)
Meno-/metrorrhagia	214 (43)
Thickened endometrium/polyp	28 (6)
Abnormal cervical smear	10
Cancer in other organs than the uterine endometrium	10
Pain	7
Suspected/palpable mass	5
Hereditary cancer disposition, HNPCC	2

HNPCC = hereditary non-polyposis colon cancer.

The study was approved as a quality assurance project by the Danish Data Protection Agency (case no.: 1-16-02-601-14) and conducted in accordance with the Helsinki Declaration and Guidelines on Good Clinical Practice.

For statistical calculations of proportions, either Fisher's exact test or the chi-squared test with Yates' correction for discontinuity was applied. Relative risk (RR) estimates were calculated with 95% confidence intervals using the approximation of Katz. For continuous variables, Student's t-test, Mann-Whitney's U-test and Wilcoxon's signed rank test were used as appropriate. Regression analysis was performed with histopathological finding as the dependent variable and age, body mass index (BMI), parity, age at menarche and co-morbidity as independent variables. The sensitivity, specificity and predictive value of vabrasio were calculated from a 2 × 2 table. The level of significance was a two-sided $p < 0.05$. Data are given as mean ± standard deviation (range) if not stated otherwise. IBM SPSS Statistics 20 was used as the statistical software.

Trial registration: not relevant. Danish Data Protection Agency: case no.: 1-16-02-601-14.

RESULTS

The clinical data and indications for vabrasio of the 503 women are shown in **Table 1** and **Table 2**. In all women but one, a histological evaluation was made; a cervical stenosis in one woman barred the physician from taking any cells. The results of the first evaluation by vabrasio are shown in **Table 3**. The incidence of insufficient and malignant results was higher in postmenopausal women than in premenopausal women.

After further diagnostic procedures, another five women were diagnosed with endometrial cancer (Table 3). These women were found among those who were diagnosed with thickened endometrium or suspected polyp (n = 17). Thus, a total of 27 women (5.4%) were found with endometrial cancers, five of whom were missed in the initial vabrasio. So, vabrasio alone for finding endometrial cancer had a sensitivity of 81%, a specificity of 100%, and predictive values of 100% (positive) and 99% (negative).

The indication for vabrasio in the 27 women with cancer was postmenopausal bleeding (n = 22), thickened endometrium/polyp (n = 3), meno/metrorrhagia (n = 1) and suspected/palpable pelvic mass (n = 1). The cancer rate on indication of postmenopausal bleeding compared with all other indications had a RR = 5.4 (range: 2.1-13.9); $p < 0.001$).

Hypertension (RR = 4.4 (range: 2.2-10.3); $p < 0.0001$), type 2 diabetes (RR = 3.9 (range: 1.7-9.1); $p < 0.004$) and hypothyroidism (RR = 5.3 (range: 2.1-13.5); $p < 0.003$) were more prevalent in women who had vabrasio and who were subsequently diagnosed with endometrial cancer than in women with no endometrial cancer. At regression analysis, age ($r = 0.12$; $p < 0.012$) and BMI ($r = 0.33$; $p < 0.001$) were positively associated with prevalence of endometrial cancer. Endometrial cancer was not found to be associated with smoking, alcohol intake, parity or age at menopause in our study population.

DISCUSSION

We found that vabrasio had a high diagnostic sensitivity and specificity for endometrial cancer. Nevertheless, five of 27 women were diagnosed with endometrial cancer after supplementary diagnostic procedures. Post-menopause substantially increased the likelihood of malignancy, but vabrasio does not always provide a sufficient sample due to stenosis of the cervix or an insufficient amount of cells. Goldberg et al compared vabrasio, curette and the D&C performed simultaneously in high-risk patients under general anaesthesia: In five out of 40 patients (12%), endometrial sampling by vabrasio was unsuccessful due to stenosis of the cervix, and sampling was insufficient for diagnosis in 4 of 35 patients (11%) [6]. Endometrial carcinoma was detected in three of the

31 women (9.7%) who had a satisfactory amount of cells in their samples. D&C found five cases of endometrial cancer in 38 samples (13%). Another study with mixed indications for sampling enrolled 147 patients and compared vabrasio with pipelle: Sampling was unsuccessful in eight women (11%) using vabrasio, and only 52.4% had a sufficient amount of cells for diagnostic use [7]. The authors further concluded that the pipelle only sampled 4.2% of the endometrium, while the vabrasio method would sample 41.6%. Thus, even in patients with high amounts of cells, sampling may be flawed by false-negative results.

The most common causes of postmenopausal vaginal bleeding were found to be genital tract atrophy (44.5-59.0%), endometrial polyps (9.2-12.0%), endometrial hyperplasia (2.0-9.9%) and endometrial carcinoma (5.0-10.0%) in three large diagnostic studies [8-10]. The decision to investigate is often complex in ascertaining whether abnormal bleeding is related to pathology or represents physiological changes. Other indications for sampling are hereditary non-polyposis colon cancer (HNPCC), women with breast cancer treated with tamoxifen, and prolonged oestrogen therapy [6, 11]. A biopsy by hysteroscopy is mandatory when episodes of bleeding in post-menopause are observed; when the endometrial thickness is greater than a certain cut-off value (in Denmark > 4 mm); and when it is not possible to determine the thickness of the endometrium [12]. In a meta-analysis of 39 studies for diagnosis of endometrial cancer in postmenopausal women, vabrasio and pipelle were both shown to have high sensitivities (97% and 99%, respectively) [5]. These figures seem rather high as insufficient and false-negative results from sampling will affect these ratios. Similarly, diagnosis of cancers depends on the background risk of the population studied and on an algorithm employed to decide which sampling tool should be used primarily. The algorithm should include ultrasound describing endometrial appearance in addition to thickness. In Scandinavian populations, an endometrial thickness of < 4 mm in postmenopausal women indicates a risk of endometrial carcinoma as low as 1% [9, 13]. As for insufficient sampling, a recent report showed similarly insufficient sampling (17%) in nearly 1,000 specimens, which underpins the challenges associated with securing a diagnosis [14].

Obesity is a risk factor for uterine cancer due to increased endogenous oestrogen levels. The risk appears to increase linearly with the degree of obesity [15]. Bjørge et al found that overweight and obese women had a RR for endometrial cancer of 1.36 and 2.51, respectively, compared with women with a normal BMI [16]. Similarly and in line herewith, women with a high BMI are younger when diagnosed with endometrial cancer: the mean age at diagnosis was 56.3 years for women with a BMI > 50 kg/m^2 and 67.1 years for women with a normal BMI [17].

Hypertension is often reported to be associated with endometrial cancer, but some dispute this correlation when hypertension is adjusted for age and BMI [18]. Similarly, a relative risk of 2.8 for endometrial cancer was reported in diabetic women compared with non-diabetic women after adjusting for age and BMI [18]. Our findings related to risk factors should be interpreted with caution. A potential information bias may have influenced the results due to the retrospective design of the study. The background data will inevitably be registered with different accuracy for women who were diagnosed with cancer or subjected to further procedures than for other women; this may apply for co-morbidity like hypertension, diabetes and hypothyroidism. On the other hand, the electronic data record aggregates all the diagnoses the woman was given previously and the medicine her general practitioner and the hospital physician prescribed. Thus, co-morbidity should be picked up by the system, at least if the condition is a chronic illness with accompanying medication.

TABLE 3

Histopathological results of the initial, diagnostic vabrasio for all women and by menopausal status. The values are n (% of column).

	All women	Postmenopausal	Premenopausal
Normal evaluation[a]	381 (76)	145 (64)[e]	236 (86)
Insufficient[b]	83 (17)	52 (23)[e]	31 (11)
Endometrial cancer	22 (4)	21 (9)[e]	1
Simple hyperplasia/polyp[c]	16 (3)	10 (4)	6 (2)
Complex hyperplasia without atypia	3	2	1
Complex hyperplasia with atypia[d]	4 (1)	4 (2)	0
Cervical cancer	1	1	0
Metastatic ovarian cancer	1	1	0
Other cancers found at clinical examination	3	2	1
Total	503	227	276

a) 2 women (1 was postmenopausal) were later diagnosed with endometrial cancer.
b) 1 postmenopausal woman had cervical stenosis and 0 cells in her sample.
c) 2 postmenopausal women were later diagnosed with endometrial cancer.
d) 1 postmenopausal woman was later diagnosed with endometrial cancer, 1 was re-diagnosed with simple hyperplasia after biopsies at hysteroscopy, and 2 were confirmed with atypical complex hyperplasia at hysterectomy.
e) Postmenopausal versus other women; p < 0.01 (chi-squared test and Fisher's exact test).

The vacuum aspirator used for histopathology assessment (vabrasio).

Infertile women have a 3-8 times greater cancer risk than fertile women [19, 20]. Infertility rather than nulliparity carries a higher risk, so parity as a risk factor for endometrial cancer is disputed. It seems that almost all risk factors are oestrogen-dependent, either considering absolute amount or time exposure, including age, late menopause and early menarche [11]. Oestrogen promotes proliferation in the endometrium, and prolonged or excessive exposure to oestrogen is viewed as a critical carcinogen [11].

CONCLUSIONS

Vabrasio has a good diagnostic sensitivity and specificity with respect to endometrial cancer, but some shortcomings due to insufficient sampling for diagnosis.

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