Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort

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Summary

Background The increase in the worldwide incidence of endometrial cancer relates to rising obesity, falling fertility, and the ageing of the population. Transvaginal ultrasound (TVS) is a possible screening test, but there have been no large-scale studies. We report the performance of TVS screening in a large cohort.

Methods We did a nested case-control study of postmenopausal women who underwent TVS in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) following recruitment between April 17, 2001, and Sept 29, 2005. Endometrial thickness and endometrial abnormalities were recorded, and follow-up, through national registries and a postal questionnaire, documented the diagnosis of endometrial cancer. Our primary outcome measure was endometrial cancer and atypical endometrial hyperplasia (AEH). Performance characteristics of endometrial thickness and abnormalities for detection of endometrial cancer within 1 year of TVS were calculated. Epidemiological variables were used to develop a logistic regression model and assess a screening strategy for women at higher risk. Our study is registered with ClinicalTrials.gov, number NCT00058032, and with the International Standard Randomised Controlled Trial register, number ISRCTN22488978.

Findings 48 230 women underwent TVS in the UKCTOCS prevalence screen. 9078 women were ineligible because they had undergone a hysterectomy and 2271 because their endometrial thickness had not been recorded; however, 157 of these women had an endometrial abnormality on TVS and were included in the analysis. Median follow-up was 5·11 years (IQR 4·05–5·95). 136 women with endometrial cancer or AEH within 1 year of TVS were included in our primary analysis. The optimum endometrial thickness cutoff for endometrial cancer or AEH was 5·15 mm, with sensitivity of 80·5% (95% CI 72·7–86·8) and specificity of 86·2% (85·8–86·6). Sensitivity and specificity at a 5 mm or greater cutoff were 80·5% (72·7–86·8) and 85·7% (85·4–86·2); for women with a 5 mm or greater cutoff plus endometrial abnormalities, the sensitivity and specificity were 85·3% (78·2–90·8) and 80·4% (80·0–80·8), respectively. For a cutoff of 10 mm or greater, sensitivity and specificity were 54·1% (45·3–62·8) and 97·2% (97·0–97·4). When our analysis was restricted to the 96 women with endometrial cancer or AEH who reported no symptoms of postmenopausal bleeding at the UKCTOCS scan before diagnosis and had an endometrial thickness measurement available, a cutoff of 5 mm achieved a sensitivity of 77·1% (67·8–84·3) and specificity of 85·8% (85·7–85·9). The logistic regression model identified 25% of the population as at high risk and 39·5% of endometrial cancer or AEH cases were identified within this high risk group. In this high-risk population, a cutoff at 6·75 mm achieved sensitivity of 84·3% (71·4–93·0) and specificity of 89·9% (89·3–90·5).

Interpretation Our findings show that TVS screening for endometrial cancer has good sensitivity in postmenopausal women. The burden of diagnostic procedures and false-positive results can be reduced by limiting screening to a higher-risk group. The role of population screening for endometrial cancer remains uncertain, but our findings are of immediate value in the management of increased endometrial thickness in postmenopausal women undergoing pelvic scans for reasons other than vaginal bleeding.

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Introduction

Endometrial cancer is the most common gynaecological cancer in Europe, and has an increasing incidence in postmenopausal women in many northern and western European countries.[1] In the UK, overall incidence of endometrial cancer increased from 13·5 per 100 000 in 1993 to 17·9 per 100 000 in 2005.[2] The increase in obesity[3] and the fall in fertility rates suggest that incidence of endometrial cancer will continue to rise in postmenopausal women, and will become a substantial public health problem worldwide.[4] This rise in incidence has implications for both primary prevention and screening.

Screening for endometrial cancer is only recommended in women with Lynch syndrome, a disorder that genetically

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predisposes women to endometrial cancer with a lifetime risk of 40–60%.[5,6] Recommended surveillance in this group includes annual transvaginal ultrasound (TVS) and endometrial biopsy from age 35 years.[7] In the general population, there has been limited enthusiasm to explore the usefulness of screening for endometrial cancer[8] because patients have a good prognosis relative to other cancers. However, in view of the rising incidence of endometrial cancer,[4] coupled with increasing life expectancy,[9] there is now a need to revisit screening. Additional factors are mortality greater than 30% within 10 years of diagnosis[10] and a proven link between stage and survival raising the possibility of a mortality benefit from earlier detection.[10] Of note, stage for stage, survival rates for endometrial cancer are similar to ovarian cancer—a cancer for which large-scale screening trials are underway.[11,12]

The techniques commonly used to assess the endometrium in symptomatic women are TVS and endometrial sampling. Few studies have been done to assess the merits of screening for detection of endometrial cancer in asymptomatic women. The largest study[13] screened 1926 postmenopausal women from the general population with TVS. One case of endometrial cancer and four cases of atypical hyperplasia were detected. Other studies[14–16] have included smaller populations, making it impossible to assess the sensitivity of screening, or to achieve confident estimates of specificity or positive predictive value.

The opportunity to study the performance of TVS in a large cohort of postmenopausal women was provided by data from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[12,17] UKCTOCS is a prospective trial of ovarian cancer screening, one arm of which involved pelvic ultrasound during which endometrial thickness was measured and recorded. This provided the opportunity to establish the performance characteristics of endometrial thickness as a possible screening test for endometrial cancer. Documentation of endometrial characteristics during TVS screening in the trial, and follow-up for cancer outcomes, provided unique data. We report on the characteristics of endometrial cancer screening in postmenopausal women in the general population to inform on the potential of screening for endometrial cancer.

Methods

Participants

We did a nested case-control study within the UKCTOCS cohort with ultrasound findings recorded at yearly screening appointments as part of the ovarian cancer screening trial. Between April 17, 2001, and Sept 29, 2005, 202 638 women were recruited to UKCTOCS from England, Wales, and Northern Ireland. The pre-identified Scottish centres dropped out because of logistical issues (lack of space, retirement of potential research leads, unwillingness of NHS Trust management to commit to a 10-year trial, involvement in other ovarian cancer screening trials).[17] Participants completed a recruitment questionnaire, which requested baseline data on lifestyle and reproductive factors, previous cancer history, and family history of breast or ovarian cancer.[17] The focus of the recruitment questionnaire was on risk factors for ovarian cancer and the trial was not resourced to collect all variables related to endometrial cancer risk at the initial visit. 50 639 participants were randomly assigned to yearly screening with TVS; 48 230 attended the initial prevalence screen and are included in our study.

All women assigned to screening with TVS who had undergone the prevalence screen were included as cases or controls. Cases were women with a confirmed diagnosis of endometrial cancer or atypical endometrial hyperplasia (AEH), complex endometrial hyperplasia (CEH), endometrial stromal sarcoma (ESS), or carcinosarcoma. The scan in the year before diagnosis was used for the analysis. When several scans had been done during this year, the scan closest to diagnosis was used. Controls were women with none of the above diagnoses during follow-up. We used the initial prevalence scan for analysis. We excluded from our study all women assigned to screening with TVS who had undergone hysterectomy before random assignment in UKCTOCS or who had no endometrial thickness measurement or recorded endometrial abnormality on the relevant scan. All participants provided written consent for the use of data in secondary studies. Our study was covered by the ethical approval obtained for the main UKCTOCS (MREC reference 00/8/34, granted by North West MREC).

Procedures

TVS with Kretz/Medison SA9900 (Medison, Seoul, South Korea) ultrasound machines was done by experienced ultrasonographers at the 13 trial centres in the UK. All sonographers had, at a minimum, a diploma in medical ultrasound or similar qualification and experience in gynaecological ultrasound. All underwent induction training, which included scanning with the national lead sonographer or one of the members of the ultrasound subcommittee before scanning on the trial. During the course of the trial, they completed an accreditation programme and attended yearly ultrasound days.

The ultrasonographers were instructed to ask about and record symptoms of postmenopausal bleeding. We do not know how accurately postmenopausal bleeding was documented and there might have been a bias to better documentation in women who had an endometrial thickness above the level which prompted clinical referral (>5 mm) according to current guidelines. In all women who reported that they had experienced any irregular bleeding to the sonographer, data were recorded on the ultrasound form. During scanning, details of ovarian morphology and size were recorded. Furthermore, endometrial thickness and pathology were recorded routinely. Representative grey-scale images of each ovary and the uterus were archived at the coordinating centre.[12]

At TVS, endometrial thickness was measured at its thickest point from the anterior to the posterior in the sagittal plane of the uterus. Callipers were placed perpendicular to the outer edge of the endometrium. If there was fluid in the endometrial cavity, the endometrial thickness was measured as above but with the inclusion of the cavity fluid and the double endometrial stripe, then the fluid diameter was subtracted at the same point. Measurements of endometrial thickness were done prospectively, but were not a criterion for intervention in the trial. In addition to measurements of endometrial thickness, details of any clinical findings were recorded. For the purposes of our study, thickened, irregular, cystic, heterogeneous, abnormal, or distended endometrium; fluid in the endometrial cavity; or polyp or other mass or lesion were included under the definition of endometrial abnormality.

In clinical practice, asymptomatic women are not investigated. However, in the presence of postmenopausal bleeding, endometrial thickness greater than 4 mm is deemed abnormal and investigated further. In the absence of any definitive data at the start of the trial, a pragmatic decision to recommend referral of asymptomatic women with an endometrial thickness greater than 10 mm was agreed on the basis of extensive discussion and consultation with clinicians. We emphasise that there was no systematic protocol-driven intervention based on endometrial thickness.

Trial guidelines for the management of endometrial thickness stated that all women with thickness greater than 5 mm should be questioned about bleeding. In the UK National Health Service, postmenopausal bleeding prompts a 2-week referral to assess for cancer, and all centres would have followed this, irrespective of measurements of endometrial thickness. Women with irregular bleeding were advised to see their family doctor so that they could be referred to a gynaecologist as part of standard clinical practice in the UK. Furthermore, the guideline recommended that asymptomatic women with thickness greater than 10 mm be considered for referral to a gynaecologist for further assessment. The guidance for asymptomatic women was the same in all of the collaborating centres. However, whether asymptomatic women were investigated further was at the discretion of the local investigator. Data on any differences between the centres are not yet available.

All participants were followed up through a flagging study with the NHS Information Centre for Health and Social Care (formerly Office of National Statistics) in England and Wales and via the Central Services Agency and Cancer Registry in Northern Ireland as appropriate. This provides regular notification of any cancer registrations or deaths in the cohort. For the purpose of this analysis, cancer registration data were obtained from the agencies on Feb 9, 2009. Women also directly informed the trial centre of a cancer when diagnosed or when they were sent an appointment for the next yearly screen. Furthermore, women who had been on the trial for 3·5 years after random assignment were sent follow-up questionnaires.

In all women where diagnoses of endometrial cancer, AEH, CEH, ESS, or carcinosarcoma were notified on

	Women without EC N=36 731	Women with EC/AEH N=136	p value
Age at random assignment (years)	60·4; 56·0–65·9 (36 731)	61·6; 56·8–66·5 (136)	0·15
Time since last period at random assignment (years)	9·6; 4·2–15·9 (36 730)	8·4; 4·2–15·3 (136)	0·51
Duration of HRT use in those who were on HRT at random assignment (years)	7·4; 4·2–10·9 (6211)	6·9; 4·6–10·6 (22)	0·96
Duration of OCP use (years)	5·0; 2·0–10·0 (21 967)	5·0; 2·0–10·0 (65)	0·55
Number of miscarriages (pregnancies <6 months)	0; 0–1 (36 218)	0; 0–1 (134)	0·18
Number of children (pregnancies >6 months)	2; 2–3 (36 632)	2; 1–3 (135)	0·0073
Height (cm)	162·6; 157·5–165·1 (36 644)	162·6; 157·5–167·6 (136)	0·14
Weight (kg)	66·7; 60·3–76·2 (36 604)	72·8; 63·5–83·5 (134)	<0·0001
Ethnic origin			0·81
White	35 459 (96·5%)	134 (98·5%)	..
Black	450 (1·2%)	1 (0·7%)	..
Asian	337 (0·9%)	0	..
Other	311 (0·8%)	0	..
Missing	174 (0·5%)	1 (0·7%)	..
Use of OCP	22 280 (60·7%)	66 (48·5%)	0·006
Use of HRT at recruitment	6211 (16·9%)	22 (16·2%)	0·99
Personal history of cancer*	2072 (5·6%)	15 (11·0%)	0·014
Personal history of breast cancer	1409 (3·8%)	9 (6·6%)	0·11

Data are median; IQR (n) or n (%). EC=endometrial cancer. AEH=atypical endometrial hyperplasia. HRT=hormone replacement therapy. OCP=oral contraceptive pill. *Includes those with personal history of breast cancer.

Table 1: **Baseline characteristics of UKCTOCS participants who underwent the first yearly scan**

	Women without EC or AEH n=36 731	Women with EC or AEH n=133	Relative risk (95% CI)
<5 mm	30 664 (83·5%)	26 (19·5%)	1
≥5 to 10 mm	4878 (13·3%)	33 (24·8%)	7·93 (4·77–13·18)
≥10 to 20 mm	1116 (3·0%)	59 (44·4%)	59·27 (37·67–93·36)
≥20 mm	73 (0·2%)	15 (11·3%)	201·2 (110·64–360·63)
Mean (SD)	3·46 mm (2·59)	11·53 mm (7·81)	..
Median (IQR)	2·9 mm (2·0–4·0)	11·0 mm (6·0–14·5)	..

Data are n (%) unless otherwise indicated. EC=endometrial cancer. AEH=atypical endometrial hyperplasia.

Table 2: **Distribution of endometrial thickness measurements in women with or without endometrial cancer or atypical endometrial hyperplasia**

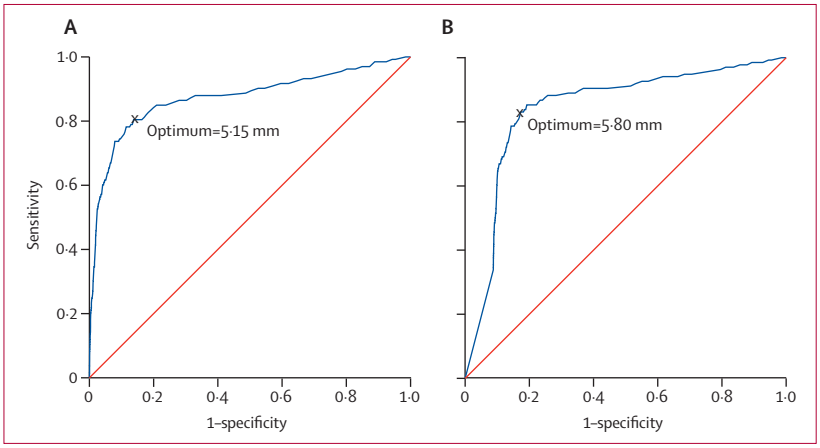

Figure 1: **Receiver operator curves for detection of endometrial cancer and atypical endometrial hyperplasia**
Endometrial thickness measurements alone (A) and a combination of endometrial thickness measurements and endometrial abnormality (B). Diagonal segments are produced by ties.

See Online for webappendix

follow-up, copies of operative notes, histopathology reports, cytology reports, discharge summaries, multidisciplinary team meeting notes, and other correspondence were obtained. The final diagnosis—which included the primary site, stage, and grade of any cancer—was made on review of the medical notes by an independent gynaecological oncologist (RM).

Our primary outcome measure was endometrial cancer and AEH. AEH was included because 40% of cases of AEH might have concurrent EC,[18] there is limited concordance between pathologists on the diagnosis of AEH or endometrial cancer,[19] and AEH is a precancerous state with greater than 25% of patients progressing to endometrial cancer (estimates range from 25% to 82%).[20–25] ESS, carcinosarcoma, and CEH were also analysed separately.

Statistical analysis

The distribution of endometrial thickness was compared in women who did and did not develop endometrial cancer or AEH. These data were used to construct a receiver operator characteristic (ROC) curve to assess the specificity and sensitivity of various thickness cutoffs for detecting endometrial cancer or AEH. A further ROC curve was constructed with both thickness and any recorded endometrial abnormality. The latter analysis included women with either endometrial thickness, endometrial abnormality, or both recorded. A multivariate logistic-regression analysis was done that combined thickness with the baseline characteristics of the study participants to develop an algorithm incorporating epidemiological variables that would identify a high-risk group who might benefit from a targeted approach to screening. Further ROC curves were constructed to assess the specificity and sensitivity of various endometrial thickness cutoffs for detecting endometrial cancer or AEH in the different risk groups.

Further analyses assessed the sensitivity and specificity profile of endometrial thickness for the detection of endometrial cancers, either alone or combined with CEH, ESS, or carcinosarcoma, with a scan done within a year of diagnosis. Subgroup analysis was by presence or absence of postmenopausal bleeding. Since there was no systematic protocol-driven intervention based on endometrial thickness, we did not analyse the data by stage of endometrial cancer.

To explore the possibility of refining screening in a higher-risk group, the baseline characteristics recorded at recruitment for women diagnosed with endometrial cancer in the control and multimodal groups of the trial were modelled as epidemiological risk factors for endometrial cancer with forward stepwise logistic regression. The significant factors and their parameter estimates were retained for a high-risk logistic-regression model. These factors were weight; age at menarche; use of the oral contraceptive pill; personal history of breast, ovarian, lung, bowel, or other cancer; age at scan; and any pregnancy of longer than 6 months (webappendix p 1). Data on the relevant variables for the ultrasound group were then inserted into the derived high-risk model and a prior risk probability of endometrial cancer was calculated solely on the basis of epidemiological data. These groups were based on the cutoffs of the ordered prior risk probabilities: the highest risk (first) quartile, the second quartile, the third quartile, and those at lowest risk (fourth quartile). Relative risks (RRs) were used because the prevalence of endometrial cancer was virtually unchanged from the prevalence of endometrial cancer in the trial population for those without hysterectomy.

Ovarian volume was assessed as another variable to identify women at higher risk of endometrial cancer or AEH by comparing measurements of those who developed endometrial cancer or AEH and those who had not.

The relative risk of endometrial cancer or AEH in women with thickness measurements of 5 mm or greater or 10 mm or greater were calculated to show the endometrial thickness cutoffs suggested by the UKCTOCS guidelines. Data were analysed with the PASW Statistics 18 package and Stata 11.0. Our study is registered with ClinicalTrials.gov, number NCT00058032, and with the International Standard Randomised Controlled Trial register, number ISRCTN22488978.

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Role of the funding source
The sponsor of the study and the funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. AG-M, MB, RM, AR, and UM also had access to the raw data.

Results

Table 1 shows the baseline characteristics of the women with and without endometrial cancer or AEH. The inclusion criteria and details of the UKCTOCS trial have been described in detail elsewhere.[12,17] 50 639 study participants were randomly assigned to the ultrasound arm of UKCTOCS. 48 230 completed the first yearly scan on the trial (prevalence screen). Of these women, 11 349 were ineligible because 9078 women had undergone a hysterectomy, and 2271 did not have endometrial thickness recorded on their scan report. 157 of the 2271 women had an endometrial abnormality reported in absence of endometrial thickness measurement and were included in our analysis. The resulting group of 37 038 women were included in our study (webappendix pp 5–6).

Median follow-up from the scan to cancer registration update was 5·11 years (IQR 4·05–5·95). Since information on cancers can take up to 3 years to be recorded on the national cancer registries, we explored other sources of follow-up data in detail in the 985 women for whom the time from scan to cancer registry follow-up on Feb 9, 2009, was less than 3 years. In this cohort, we had additional confirmation of endometrial cancer status in 849 women because they had attended further screening and in 66 of the remaining women through returned follow-up questionnaires. In 70 of 37 038 women, the only source of information on endometrial cancer status was cancer registry follow-up of less than 3 years from the date of scan.

The cohort of 37 038 women includes 125 women who developed endometrial cancer after random assignment (100 endometrioid [80%], six papillary serous [5%], two clear cell [2%], three mixed subtype [2%], one mucoid [1%], and 13 endometrial carcinoma without specification of histological subtype [10%]), six with ESS, six with carcinosarcomas or mixed Müllerian tumours, 11 with AEH, and two with CEH. 133 of the 136 women with endometrial cancer or AEH had endometrial thickness measurements recorded and three had endometrial abnormalities. 96 of the 125 women who

	Measure	Number of cases	Area under curve (95% CI)	>5 mm ET cutoff				>10 mm ET cutoff				Optimum cutoff				
				n	Sensitivity (95% CI)	n	Specificity (95% CI)	n	Sensitivity (95% CI)	n	Specificity (95% CI)	Cutoff (mm)	n	Sensitivity (95% CI)	n	Specificity (95% CI)
EC+AEH	ET	133	0·872 (0·834–0·912)	107	0·805 (0·727–0·868)	31478	0·857 (0·854–0·862)	72	0·541 (0·453–0·628)	35703	0·972 (0·970–0·974)	5·15	107	0·805 (0·727–0·868)	31662	0·862 (0·858–0·866)
EC+AEH	ET+EA	136	0·844 (0·811–0·878)	116	0·853 (0·782–0·908)	29657	0·804 (0·800–0·808)	89	0·654 (0·568–0·734)	33051	0·896 (0·893–0·899)	5·80	113	0·831 (0·757–0·890)	30506	0·827 (0·823–0·831)
EC+AEH (HRT only)	ET	22	0·901 (0·842–0·959)	19	0·864 (0·651–0·971)	4676	0·753 (0·742–0·764)	11	0·500 (0·282–0·718)	6030	0·971 (0·967–0·975)	6·85	17	0·773 (0·546–0·922)	5459	0·879 (0·871–0·887)
EC+AEH (HRT only)	ET+EA	23	0·864 (0·808–0·920)	20	0·870 (0·664–0·972)	4454	0·715 (0·704–0·726)	12	0·522 (0·306–0·732)	5682	0·912 (0·905–0·919)	6·85	18	0·783 (0·563–0·925)	5177	0·831 (0·822–0·840)
EC+AEH (non-HRT only)	ET	111	0·868 (0·823–0·913)	88	0·793 (0·705–0·864)	26889	0·881 (0·877–0·885)	61	0·550 (0·452–0·644)	29666	0·972 (0·970–0·974)	4·55	92	0·829 (0·746–0·894)	25577	0·838 (0·834–0·842)
EC+AEH (non-HRT only)	ET+EA	113	0·839 (0·801–0·877)	96	0·850 (0·770–0·910)	25231	0·823 (0·819–0·827)	77	0·681 (0·587–0·766)	27377	0·893 (0·889–0·896)	5·15	96	0·850 (0·770–0·910)	25323	0·826 (0·822–0·830)
EC+AEH+CEH+ESS or carcinosarcoma	ET	147	0·873 (0·836–0·910)	117	0·796 (0·722–0·858)	31515	0·858 (0·854–0·862)	80	0·544 (0·460–0·626)	35703	0·972 (0·970–0·974)	5·15	117	0·796 (0·722–0·858)	31662	0·862 (0·858–0·866)
EC+AEH+CEH+ESS or carcinosarcoma	ET+EA	150	0·844 (0·812–0·876)	127	0·847 (0·779–0·900)	29657	0·804 (0·800–0·808)	99	0·660 (0·578–0·735)	33051	0·896 (0·893–0·899)	5·15	127	0·847 (0·779–0·900)	29805	0·808 (0·804–0·812)

The analysis was done separately for endometrial thickness (ET) alone (no women who had no ET measurements were included) and for ET and endometrial abnormality (EA). In the latter analysis, the 157 women in the overall cohort who had no ET recorded, but had an EA recorded, were included. In ET+EA measure all EA cases count as maximum ET—ie, always positive. n=number. EC=endometrial cancer. AEH=atypical hyperplasia. HRT=hormone replacement therapy. CEH=complex hyperplasia. ESS=endometrial stromal sarcoma.

Table 3: **Performance characteristics of endometrial thickness as a screening tool for endometrial cancer with and without endometrial abnormality**

developed endometrial cancer after random assignment were stage 1, 11 were stage 2, nine were stage 3, and one was stage 4. Data on stage were not available for eight women. Overall, 112 of the 136 women with endometrial cancer or AEH were asymptomatic and 24 were symptomatic at the last UKCTOCS scan before diagnosis (of 99 women with endometrial cancer or AEH who reported no postmenopausal bleeding, 96 had endometrial thickness measurements available).

The remainder of the cohort is 36888 controls, who are women without a diagnosis of endometrial cancer or AEH within 1 year of their last UKCTOCS scan. The control group includes six women who had either a leiomyosarcoma or breast cancer that was metastatic to the endometrium and 23 women who had endometrial cancer or AEH diagnosed more than 1 year after the last UKCTOCS scan. 36731 of the women in the control group had endometrial thickness measurements and the remaining 157 had endometrial abnormalities recorded. In 2271 (5·5%) of 41561 women with an intact uterus, data on endometrial thickness were missing. The 5% missing data rate is in keeping with what was anticipated for a study of this type and size.

Weight, age, and personal history of cancer were associated with an increased risk of endometrial cancer or AEH, although oral contraceptive pill, age at menarche, and parity were associated with a decreased risk (webappendix p 1).

Table 2 shows the distribution of endometrial thickness measurements in the 36731 women who did not have a diagnosis of endometrial cancer or AEH. Most of the women had an endometrial thickness of less than 5 mm. In the 133 women with a diagnosis of endometrial cancer or AEH who had endometrial thickness recorded, 107 (81%) had an endometrial thickness of 5 mm or greater. There was a significant difference between endometrial thickness in women with and without endometrial cancer or AEH (p<0·0001). The optimum cutoff for endometrial thickness was 5·15 mm with a RR of 25·2 (95% CI 16·5–38·5).

The webappendix (p 2) shows the distribution of endometrial thickness measurements according to the use of hormone replacement therapy (HRT) in the overall cohort. The median endometrial thickness in women in the whole cohort who did not use HRT was 2·7 mm (IQR 2·0–3·95) versus 3·6 mm (2·5–5·1) in women that did and these results were similar in the subgroup of women without endometrial cancer or AEH (p<0·0001). By contrast, the median thickness was 11·0 mm (5·9–14·8 without HRT; 7·0–14·5 with HRT) in women with endometrial cancer or AEH, irrespective of the use of HRT.

1406 women reported breast cancer diagnosis before entry into the trial. These women were more likely to have an endometrial thickness of 5 mm or greater to less than 10 mm (RR 1·91; 95% CI 1·68–2·18), 10 mm or greater to less than 20 mm (4·50; 3·85–5·25), and 20 mm or greater (11·01; 8·04–14·47) than women with no history of breast cancer (webappendix, p 3). Of the women with no history of breast cancer, 29757 (83·9%) of 35460 had an endometrial thickness of less than 5 mm compared with 940 (66·9%) of 1406 women with history of breast cancer—the median endometrial thickness was 2·9 mm versus 3·6 mm (p<0·0001; webappendix p 3). A large proportion of this measurement in women with breast cancer was probably related to tamoxifen use, but treatment data were not systematically captured as part of the trial.

We did an analysis of endometrial thickness by screening centre in the women who did not develop endometrial cancer. The median endometrial thickness was 2·9 mm. The median thickness varied from 2·1 mm to 3·4 mm

	Overall		Positive for bleeding		Negative for bleeding	
	Number	% (95% CI)	Number	% (95% CI)	Number	% (95% CI)
5 mm cutoff						
>5 mm	107	..	33	..	74	..
≤5 mm	31464	..	54	..	31410	..
Sensitivity	..	80·5% (72·7–86·8)	..	89·2% (76·9–95·6)	..	77·1% (67·8–84·3)
Specificity	..	85·7% (85·4–86·2)	..	42·2% (38·6–44·0)	..	85·8% (85·7–85·9)
Positive predictive value	..	2·0% (1·8–2·1)	..	30·8% (26·6–33·1)	..	1·4% (1·2–1·5)
Negative predictive value	..	99·9% (99·9–99·9)	..	93·1% (85·2–97·2)	..	99·9% (99·9–100)
10 mm cutoff						
>10 mm	72	..	24	..	48	..
≤10 mm	35746	..	99	..	35586	..
Sensitivity	..	54·1% (45·3–62·8)	..	64·9% (51·0–76·7)	..	50·0% (40·3–59·7)
Specificity	..	97·2% (97·0–97·4)	..	77·3% (73·4–80·8)	..	97·2% (97·1–97·3)
Positive predictive value	..	6·4% (5·4–7·4)	..	45·3% (35·7–53·5)	..	4·5% (3·6–5·4)
Negative predictive value	..	99·8% (99·8–99·9)	..	88·4% (83·8–92·3)	..	99·9% (99·8–99·9)

Table 4: **Performance characteristics of endometrial thickness as a screening tool for endometrial cancer in women with and without postmenopausal bleeding**

across the regional centres. All but three centres had a median thickness within 0·3 mm of the overall median thickness. When dichotomised as endometrial thickness less than 5 mm and 5 mm or greater, the proportion of measurements greater than 5 mm per centre varied from 10·4% to 22·4% (overall proportion 16·8%; median centre proportion 16·6%, IQR 14·7–19·8).

To assess the sensitivity and specificity profile for detection of endometrial cancer or AEH, a ROC curve was constructed with cutoff points for endometrial thickness with or without data for endometrial abnormalities (figure 1, webappendix p 4). Table 3 shows the sensitivities and specificities at 5 mm and 10 mm cutoffs and shows the optimum cutoffs. A separate ROC curve was constructed incorporating endometrial abnormality findings in addition to thickness measurements (figure 1, table 3). Use of endometrial abnormality findings and thickness measurements at a cutoff of 5 mm or greater increased sensitivity but decreased specificity. The same effect was noted at a cutoff of 10 mm or greater (figure 1, table 3). In asymptomatic women the optimum endometrial thickness cutoff was 4·45 mm.

Table 3 shows analyses of combined endometrial cancer, AEH, CEH, and sarcomas. Our subgroup analyses that included endometrial cancer and AEH or a combination of endometrial cancer, AEH, CEH, and ESS or carcinosarcoma showed similar levels of sensitivity and specificity.

Given the difference noted in endometrial thickness distribution in users of HRT and non-users, the optimum cutoff in HRT users was as expected higher (6·85 mm) than non-users (4·55 mm; table 3).

At the UKCTOCS scan, postmenopausal bleeding was recorded in 165 women (37 cases and 128 controls). Table 4 shows the performance characteristics for women with and without postmenopausal bleeding.

The relation between ovarian volume and endometrial cancer or AEH was assessed and no statistically significant correlation was identified (p=0·956; data not shown).

We explored the possibility of optimising approaches to endometrial cancer screening by incorporating epidemiological information provided in the recruitment questionnaire. Logistic regression showed that decreased endometrial cancer or AEH risk was associated with the use of the oral contraceptive pill, age at menarche, and pregnancies longer than 6 months, while increased risk was associated with rising weight, increasing age, and personal history of breast and other cancer (multivariate and univariate analyses are shown in webappendix p 1). On the basis of the logistic regression model, the population could be divided into quartiles with RRs for endometrial cancer compared with the entire population of 1·98 (1·39–2·80) for the first quartile, 1·07 (0·73–1·58) for the second, 0·76 (0·49–1·16) for the third, and 0·49 (0·30–0·79) for the fourth (table 5). The population in the highest quartile of risk (first quartile) included 39·5% of women with endometrial cancer or AEH; in this population an optimum endometrial thickness cutoff at 6·75 mm achieved a sensitivity of 84·3% and specificity of 89·9% (figure 2, table 5).

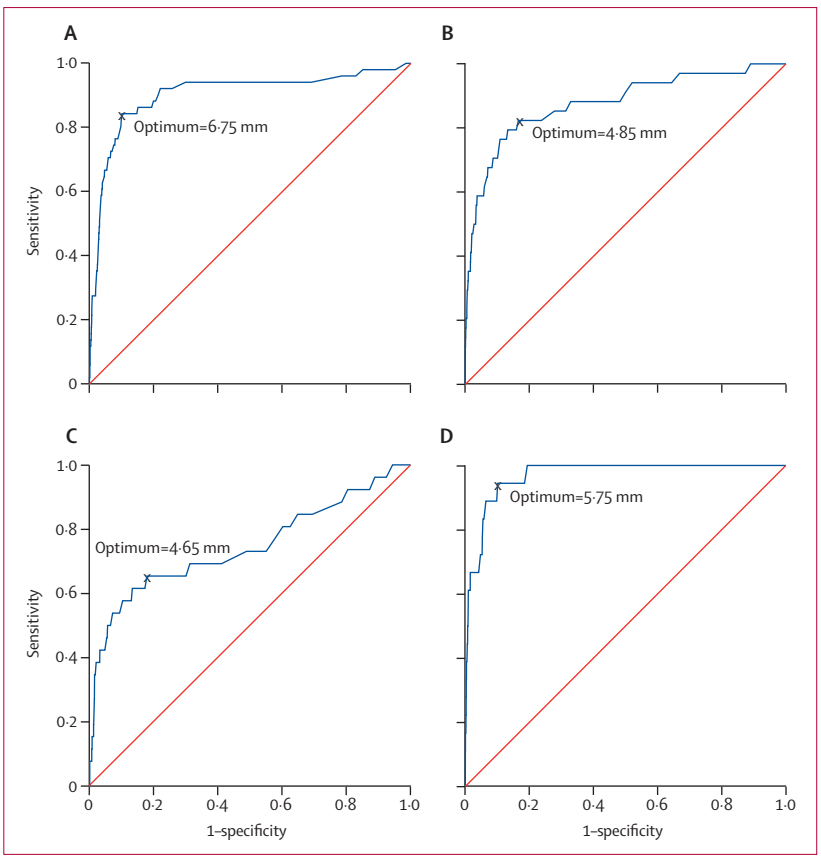

Figure 2: **Receiver operator curve for endometrial thickness measurements for detection of endometrial cancer in the high-risk group**
First quartile (A), second quartile (B), third quartile (C), and fourth quartile (D). Diagonal segments are produced by ties.

We also assessed the number of further interventions that would be predicted if endometrial thickness measurements were used as a screen for endometrial cancer or AEH (table 6). If the entire population were screened, an endometrial thickness cutoff of 5 mm or greater would result in 58 women undergoing further investigation per case of endometrial cancer or AEH detected for the diagnosis of 80·5% (107 of 133) of cancers. A cutoff of 10 mm or greater, would lead to 17 women being investigated to detect each case of endometrial cancer (55·6% [74 of 133 cancers diagnosed]). The number of investigations per case of endometrial cancer or AEH for the optimum cutoff of 5·15 mm was 47·7 (data not shown). If the proportion of the population screened was reduced by the use of our logistic regression model to limit screening to the top quartile risk group, 22 women would have to undergo investigation per endometrial cancer detected for the detection of 43 (32·3%) cases in the entire population.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial currently underway in the USA,[11] has

	Number of cases/ controls	Proportion of cases included	RR of EC (95% CI)	Area under curve (95% CI)	>5 mm ET cutoff				>10 mm ET cutoff				Optimum cutoff				
					n	Sensitivity (95% CI)	n	Specificity (95% CI)	n	Sensitivity (95% CI)	n	Specificity (95% CI)	Cutoff	n	Sensitivity (95% CI)	n	Specificity (95% CI)
First quartile	51/9015	39·5%	1·98 (1·39–2·80)	0·902 (0·848–0·957)	44	0·863 (0·737–0·943)	7546	0·837 (0·829–0·845)	32	0·627 (0·481–0·759)	8654	0·960 (0·956–0·964)	6·75 mm	43	0·843 (0·714–0·930)	8104	0·899 (0·893–0·905)
Second quartile	34/9081	26·4%	1·07 (0·73–1·58)	0·878 (0·808–0·948)	27	0·794 (0·621–0·913)	7846	0·864 (0·857–0·871)	16	0·471 (0·298–0·649)	8863	0·976 (0·973–0·979)	4·85 mm	28	0·824 (0·655–0·932)	7574	0·834 (0·826–0·842)
Third quartile	26/9104	20·2%	0·76 (0·49–1·16)	0·744 (0·623–0·865)	16	0·615 (0·406–0·798)	7839	0·861 (0·854–0·868)	10	0·385 (0·202–0·594)	8867	0·974 (0·970–0·977)	4·65 mm	17	0·654 (0·443–0·828)	7456	0·819 (0·811–0·827)
Fourth quartile	18/9115	14·0%	0·49 (0·30–0·79)	0·969 (0·947–0·991)	17	0·944 (0·727–0·999)	7948	0·872 (0·865–0·879)	12	0·667 (0·410–0·867)	8914	0·978 (0·975–0·981)	5·75 mm	17	0·944 (0·727–0·999)	8194	0·899 (0·893–0·905)

n=number. RR=relative risk. EC=endometrial cancer. ET=endometrial thickness.

Table 5: **Performance characteristics of endometrial thickness as a screening tool for endometrial cancer by quartile risk groups**

recruited 78 237 postmenopausal women of whom 34 261 will undergo screening with both cancer antigen 125 for 5 years and TVS for 3 years. The ultrasound findings have shown that ovarian volume greater than 3 cm^3 could be used as a variable to identify women at higher risk of endometrial cancer or AEH. When we assessed this in our cohort, we found that for the left ovary, the use of the suggested cutoff of 3 cm^3, the p value was 0·063 and for the right ovary p was 0·218.

Discussion

Ultrasound imaging of the endometrium has long been thought a possible screening test for endometrial cancer. However, there has been a dearth of data about the performance of potential tests and the largest study involved fewer than 2000 women and only one endometrial cancer was diagnosed.[13] The UKCTOCS protocol enabled us to assess the performance of TVS in screening for endometrial cancer in 37 038 postmenopausal women. With an endometrial thickness cutoff of 5 mm, sensitivity was 80·5% and specificity was 85·7% for endometrial cancer or AEH. An increased cutoff of 10 mm or greater resulted in a reduced sensitivity and increased specificity (table 3). When the analysis was restricted to women who reported no symptoms of postmenopausal bleeding at the scan and had an endometrial thickness measurement available, a cutoff of 5 mm achieved a sensitivity of 77·1% and specificity of 85·8% (table 4). Although the role of population screening for endometrial cancer remains uncertain, the findings are of immediate value in the management of increased endometrial thickness in postmenopausal women undergoing pelvic scans for reasons other than vaginal bleeding.

Our findings confirm the strong correlation between TVS findings and subsequent diagnosis of endometrial cancer, as shown by the RRs (table 2). The RR for a cutoff of 5·15 mm was 25·2. The optimum cutoff in the high-risk group was 6·75 mm, with an RR of 43·73. This correlation was shown by the levels of sensitivity for the detection of endometrial cancer or AEH, which were in the range of 80–85% depending upon the target

	ET cut-off (mm)	Number of cases of EA/AEH with positive result	Proportion of EC cases detected	Number of women with positive result	Risk of EC/AEH	Relative risk of EC/AEH (95% CI)	Number of investigations per case detected
Whole population screened	>0	133	100·00%	36 864	0·36%	1·00	277
Whole population screened	≥5	107	80·45%	6174	1·73%	20·47 (13·39–31·30)	58
Whole population screened	≥10	74	55·64%	1263	5·86%	35·37 (25·84–49·50)	17
Whole population screened	≥20	15	11·28%	88	17·05%	53·15 (32·11–85·00)	6
First quartile (highest risk) screened	>6·75	43	32·33%	954	4·51%	43·73 (20·99–90·32)*	22
Second quartile screened	>4·85	28	21·05%	1535	1·82%	22·63 (9·64–53·19)*	55
Third quartile screened	>4·65	17	12·78%	1665	1·02%	8·38 (3·82–18·40)*	98
Fourth quartile (lowest risk) screened	>5·75	17	12·78%	938	1·81%	145·88 (24·81–860·25)*	55

*Relative risk within the risk quartile. EC=endometrial cancer. AEH=atypical endometrial hyperplasia. ET=endometrial thickness.

Table 6: **Number of further interventions predicted if endometrial thickness measurements were used to screen for EC/AEH**

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population and screening criteria applied. As expected, the optimum cutoff in asymptomatic women of 4·45 mm is similar but lower than the 5 mm cutoff reported for symptomatic women.[26]

Of note, our report shows that 26 women (19·5%) who developed endometrial cancer within a year of their scan on UKCTOCS had an endometrial thickness of less than 5 mm. In a theoretical model, based on the estimate that 15% of endometrial cancers occur in women without vaginal bleeding, Smith-Bindman and colleagues[27] calculated the risk of endometrial cancer to be 6·7% for an endometrial thickness greater than 11 mm.[27] This fits satisfactorily with 5·9% risk of endometrial cancer in our cohort where 96 (72·2%) of 133 women were asymptomatic at an endometrial cutoff of 10 mm.

Although the data show that TVS can detect endometrial cancer before symptoms are detected in a high proportion of postmenopausal women, there are a range of issues that need to be addressed before population screening for endometrial cancer can be proposed. One important issue, which is not addressed in our analysis, is the effect of endometrial screening on survival or mortality from the disease. However, the answer to this question will be extremely difficult to establish even for a test with 100% sensitivity. If we assume an incidence of 60 per 100 000 per year and 30% mortality at 5-year follow-up, a randomised controlled trial would need 500 000 participants to document a 50% reduction in mortality. Since a trial on this scale is almost certainly not feasible, decisions about whether or not to screen for endometrial cancer will have to be made on the basis of surrogate measures of efficacy. Two important considerations are the overall burden of population screening and the consequences of false-positive results. We explored the possibility of reducing the overall burden of screening by focusing on a group of the population identified as being at higher risk on the basis of epidemiological criteria. Our logistic regression model that used epidemiological variables of the use of the oral contraceptive pill, age at menarche, number of pregnancies, weight, age, and history of cancer was able to separate the population into quartile groups at different levels of risk. With this approach, the highest risk quartile included almost 40% of endometrial cancer or AEH cases. In this group, an endometrial thickness cutoff at 6·75 mm achieved a sensitivity of 84·3% and a specificity of 89·9%. This would reduce the burden of screening to 25% of the population with detection of about 40% of the cases.

The strengths of our study include the large size of our cohort, prospective data collection with standardised measurement of endometrial thickness as part of the trial protocol, systematic follow-up, and information on epidemiological variables. Consistent with earlier reports of the correlation of endometrial thickness and HRT,[28] the median endometrial thickness in users of HRT in the control group was 3·6 mm versus 2·7 mm in non-users. Median endometrial thickness was also significantly greater in those with a history of breast cancer when compared with women with no history. This probably relates to the use of tamoxifen, which is known to be associated both with increased endometrial thickness (range 4·9–11·7 mm) in postmenopausal women[29–34] and increased risk of endometrial cancer (rates of 0·3% *vs* 0·06% in women on placebo).[35] We were, however, unable to confirm a recently reported correlation between ovarian volume and the risk of endometrial cancer of AEH reported by the PLCO trialists.[36]

One of the limitations of our study was that endometrial cancer screening was not an interventional endpoint in the UKCTOCS. Guidelines were provided based upon current practice in the UK, but the final decision was at the clinician's discretion. The lack of systematic protocol-driven intervention on the basis of endometrial thickness meant that we could not assess the data by stage of endometrial cancer. Detailed data on the variety of procedures done was not collected, but this is unlikely to alter the performance characteristics of endometrial thickness.

A further limitation of our study is the accuracy of the reports of postmenopausal bleeding. Although sonographers were instructed to ask about and record symptoms of postmenopausal bleeding, we do not know if these data were recorded accurately. Therefore, there might be bias in the recording of these data for women who had an endometrial thickness above the level that triggered clinical referral (>5 mm).

There was a difference in median endometrial thickness measurements in healthy women across the 13 centres. There are no previous data on variation in thickness measurements across different sonographers. Our findings accord with the only study we are aware of that included 48 postmenopausal women who were scanned by two examiners. In this cohort, the mean interobserver difference for the same woman was 0·2 mm (SD 1·9).[37] Our variation is probably multifactorial. In addition to slight variations in the scanning techniques for measuring endometrial thickness in 36 731 individuals across 13 centres, it is also probably related to variations in the demographics such as body-mass index of patients between centres. It highlights the need to have training and quality assurance measures in place if ultrasound were to be used as a screen for endometrial cancer.

The CIs around parameter estimates were wide because of low numbers of endometrial cancers despite the large overall number of participants. Some key variables that could affect risk of endometrial cancer, such as smoking,[38] diabetes, and hypertension,[39] could not be used in model building because the main focus of the recruitment questionnaire was on risk factors for ovarian cancer. Variables were collected on follow-up and a greater percentage of women with endometrial cancer reported a history or diagnosis of diabetes (nine [10·2%] of 88) compared with those without endometrial

Panel: **Research in context**

Systematic review

A systematic review of ovarian cancer screening[41] was published by the NHS Centre for Reviews and Dissemination before submission of the grant proposal to the UK Medical Research Council for United Kingdom Collaborative Trial of Ovarian Cancer Screening. No systematic review of endometrial cancer screening was done.

A detailed review of published work of endometrial cancer screening in an asymptomatic population was done as part of our analysis. We searched PubMed in February, 2010, with the terms "endometrial cancer", "screening", "endometrial thickness", and "asymptomatic". Our search was limited to papers in English. The largest study[13] involved the TVS screening of 1926 postmenopausal women in the general population. One case of endometrial cancer and four cases of atypical hyperplasia were detected. Other studies[14–16] have included smaller populations making it impossible to assess the sensitivity of screening or to achieve confident estimates of specificity or positive predictive value.

Interpretation

Our study provides to our knowledge the only large-scale data on the performance characteristics of TVS in endometrial cancer screening, and provides evidence that ultrasonography can detect endometrial cancer in asymptomatic women with 80–90% sensitivity and similar levels of specificity. Our findings provide the basis for further studies to assess the acceptability, health economics, and risk stratification. Clinicians faced with ultrasound data on endometrial thickness from scans done in various disorders aside from vaginal bleeding will now have data to inform their daily practice.

cancer (1429 [5·0%] of 28 801; data not shown). Incorporation of these factors and family history of endometrial cancer might have substantially improved the value of the high-risk score and should be assessed in future studies. Furthermore, although there was an association with weight, we could not confirm the link between the risk of endometrial cancer and body-mass index.[40] A paucity of detailed information on type of HRT and duration of use at scan also reduced our ability to do further subanalyses.

False-positive results on TVS screening for endometrial cancer will require a form of endometrial sampling that, although not a major procedure, will generate anxiety, inconvenience, and cost. There are of course complications as well as costs of hysteroscopy that would need to be assessed carefully in a risk-benefit analysis if screening for endometrial cancer with TVS was to be introduced. We do not have data on complications of hysteroscopy available for this dataset. Another important consideration for future studies of endometrial cancer screening is acceptability of the screening strategy.

A cutoff at 5 mm or greater would result in 58 diagnostic procedures for each case of endometrial cancer detected. Although the number of false positives can be reduced substantially by increasing the cutoff, this results in a corresponding fall in sensitivity. For a cutoff of 10 mm or more, sensitivity fell from 81% to 56% with the number of investigative procedures decreasing from 58 to 17. Of note, hysteroscopy—the investigation used to follow-up an abnormal endometrial cancer screen result—is of low morbidity and cost and often done as an outpatient procedure. The consequence of false-positive endometrial cancer screening findings is probably substantially less than in ovarian cancer where the consequence is abdominal surgery by laparoscopy or laparotomy. A targeted screening approach might help reduce the overall number of false-positive findings while maintaining a high sensitivity. We are exploring the possibility of further refining risk stratification by incorporating sex-steroid hormone profiling.

Whether ovarian cancer screening will save lives is currently unclear and whether the primary screen should be with TVS or a serum biomarker is debated. Nevertheless, the potential for integrating endometrial cancer with ovarian cancer screening will be clearer once UKCTOCS has reported. The extra cost of incorporating endometrial cancer screening within the scope of an ovarian cancer screening trial could be marginal and add benefit to the screening strategy if properly modelled.

Our report is to our knowledge the first large-scale report of the performance characteristics of TVS in endometrial cancer screening (panel). It forms the basis for further studies and is not intended to answer all the questions that arise. In particular, issues of early detection, morbidity, acceptability, and health economics of intervening on the basis of endometrial thickness will need to be the subject of future studies. Any comment on the likely benefit of detection of endometrial cancer by ultrasound screening would be conjecture. We have limited ourselves to reporting and discussing the performance characteristics.

The rising incidence of endometrial cancer and the difficulty of doing a randomised controlled trial large enough to specify mortality as an endpoint, suggests that the decision to introduce screening for all or a subgroup of asymptomatic women will rest on surrogate criteria such as the performance characteristics described in our report and future studies of acceptability, health economics, and risk stratification. We do not advocate population screening for endometrial cancer until further data are available from these studies.

Contributors

IJJ, AGM, MB, SC, and UM contributed to the study design, analysis and interpretation of the data, and drafting and revision of the report. IJ, UM, and AGM did the search of published work. IJ, MB, and AGM prepared the figures and tables. IJ, MB, and AGM did the statistical analysis. NS and RM contributed to the confirmation of the endometrial cancer diagnoses and the interpretation of the data. SC contributed to the interpretation of the data. All authors critically revised the report and approved the final version. IJ is the guarantor.

Conflicts of interest

IJ has a consultancy arrangement with Becton Dickinson relating to tumour markers and ovarian cancer. UM and IJ has a financial interest through UCL Business and Abcodia Ltd in the third party exploitation of clinical trials biobanks, which have been developed through the research at UCL. All other authors declared no conflicts of interest.

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