Transvaginal Ultrasound Measurement of Endometrial Thickness as a Biomarker for Estrogen Exposure

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Abstract

Objective: In clinical settings, transvaginal ultrasound has been used to evaluate abnormal vaginal bleeding. Because the endometrium responds to estrogens, endometrial thickness may constitute a biomarker of estrogen status in postmenopausal women. This study aimed to validate the transvaginal ultrasonographic measurement of endometrial thickness as an estrogen biomarker in asymptomatic, postmenopausal women by demonstrating an association between endometrial thickness and risk factors known to be associated with estrogen exposure. Method: Endometrial thickness was measured in 1,271 women ages 55 to 74 years who underwent transvaginal ultrasound screening as part of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. A questionnaire, completed before screening, provided risk factor information, including reproductive and hormone use histories. Results: Endometrial thickness measurements ranged from 1 to 32 mm (median 3.0 mm). The frequencies of thicker endometrium (≥3.0 mm), according to body mass index (BMI) quartile, were 55.2%, 66.1%, 69.7%, and 76.7% ($P < 0.0001$). The frequencies of thicker endometrium were 57.8%, 58.3%, and 82.6% among never users, ex-users, and current users of hormone replacement therapy (HRT), respectively ($P < 0.0001$). Other factors associated with thicker endometrium included age, marital status, history of uterine fibroids, years since menopause, and history of hypertension. Statistically significant associations were not seen in analyses limited to current HRT users ($n = 461$). In multiple variable analysis ($R^2 = 0.08$), current HRT use ($P < 0.0001$) and higher BMI ($P < 0.0001$) were independently associated with thicker endometrium. Conclusion: In postmenopausal women, factors reflecting exogenous (current HRT use) and endogenous (BMI) estrogen exposure were associated with increased endometrial thickness as measured during screening transvaginal ultrasound. Practical limitations related to screening transvaginal ultrasound include measurement variability, lack of information regarding type or dose of HRT, and problems of differentiating true endometrial thickening from unrecognized endometrial polyps or fluid accumulations. Constrained by these limitations, these results partially validate a transvaginal ultrasound measurement of endometrial thickness as a potential biomarker related to estrogen status. (Cancer Epidemiol Biomarkers Prev 2004;13(9):1459–65)

Introduction

Transvaginal ultrasound is a noninvasive diagnostic tool commonly used to evaluate women with postmenopausal uterine bleeding. The ultrasound examination for endometrial pathology includes a measurement of endometrial thickness. In clinical studies, endometrial malignancy is uncommon in women with an endometrial thickness measurement <5 mm (1, 2).

In contrast, this study specifically evaluates transvaginal ultrasound measurements of endometrial thickness in generally asymptomatic postmenopausal women, not selected for symptoms of uterine pathology. Because the endometrium contains estrogen receptors and responds to circulating estrogens (3), endometrial thickness constitutes a potential biological marker of estrogen status even in postmenopausal women. To the extent that transvaginal ultrasound effectively measures endometrial thickness and estrogen status, endometrial thickness measurements may function as a useful biomarker for study of hormone-related malignancy, including breast, ovarian, endometrial, and even colon cancer. However, because the endometrium atrophies after menopause, errors associated with the transvaginal ultrasound measurement of endometrial thickness may be large relative to the variation in endometrial thickness observable across postmenopausal women at risk for estrogen-related malignancy. To address this concern, this study aimed to validate the transvaginal ultrasound measurement of endometrial thickness in generally asymptomatic, postmenopausal women by demonstrating relationships between endometrial thickness measurements and factors known to be associated with estrogen exposure.

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Methods

Study Population. The study group included female participants at the Pittsburgh Center for the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (4, 5). PLCO is a National Cancer Institute

randomized clinical trial testing the effectiveness of early prostate, lung, colorectal, and ovarian cancer detection with (*1*) digital rectal examination and prostate-specific antigen blood testing, (*2*) chest X-ray, (*3*) flexible sigmoidoscopy, and (*4*) transvaginal ultrasound and CA-125 blood testing, respectively (4, 5). PLCO used community-directed mass mailings to recruit 55- to 74-year-old men and women with no personal history of prostate, lung, colorectal, or ovarian cancer. Criteria for exclusion included (*1*) current treatment for cancer, (*2*) prior total colectomy or pneumonectomy, (*3*) participation in another cancer screening or primary prevention study, and (*4*) recent tamoxifen use.

Figure 1 provides a detailed account of the first 4,328 women enrolled from November 1993 to November 2000 at the Pittsburgh PLCO Screening Center and assigned to the screening intervention. Of these 4,328 women, 1,632 were not candidates for screening transvaginal ultrasound because of a personal history of hysterectomy or bilateral oophorectomy. An additional 368 had not had any transvaginal ultrasound screening examinations done on or before June 15, 2000, the closure date for this study. In 41 instances, examiners were not able to insert the vaginal probe.

Although PLCO did not record endometrial thickness as part of the ovary cancer screening examination,

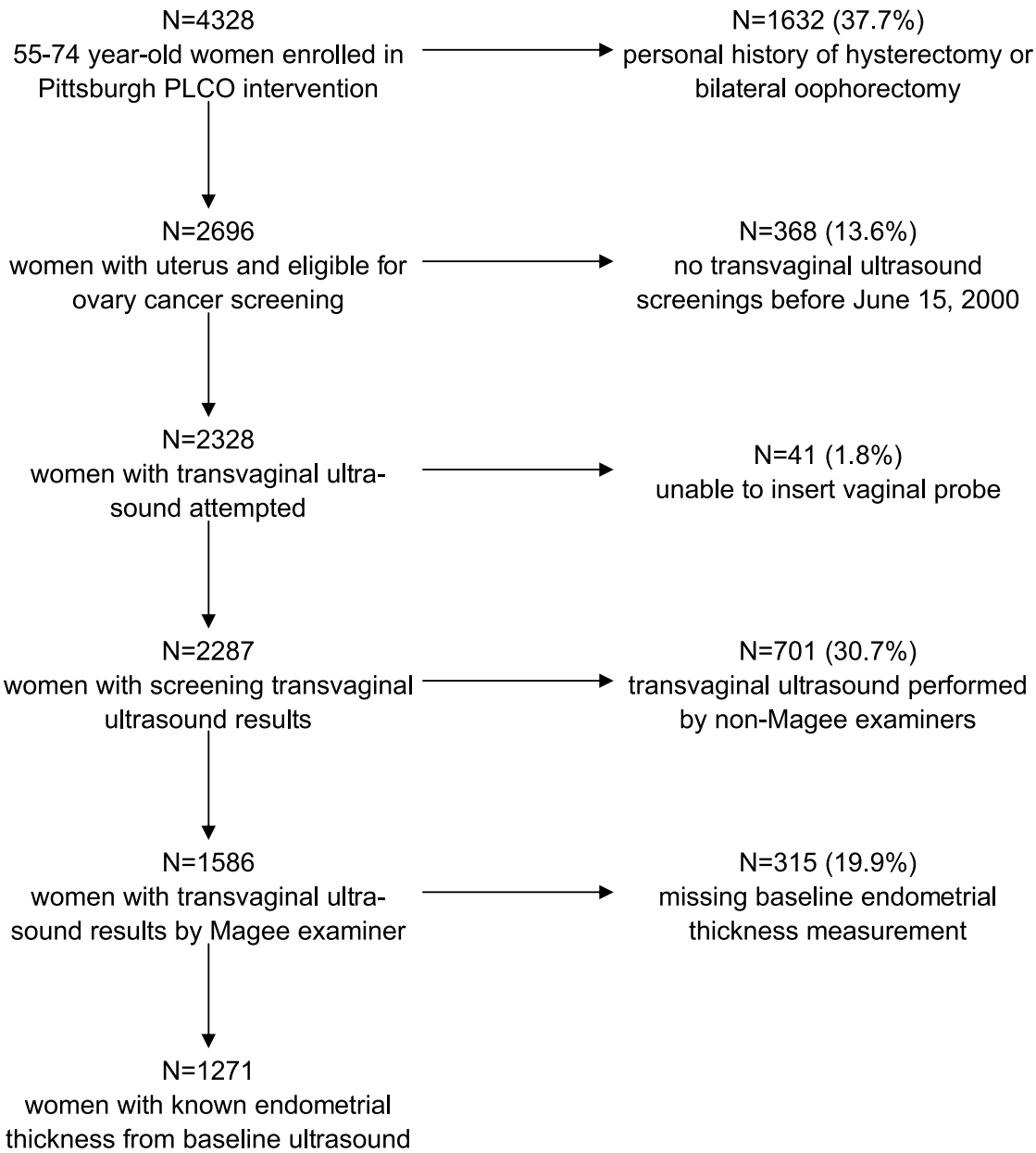

Figure 1. Detailed account of the first 4,328 women enrolled at the Pittsburgh PLCO Screening Center and assigned to the screening intervention.

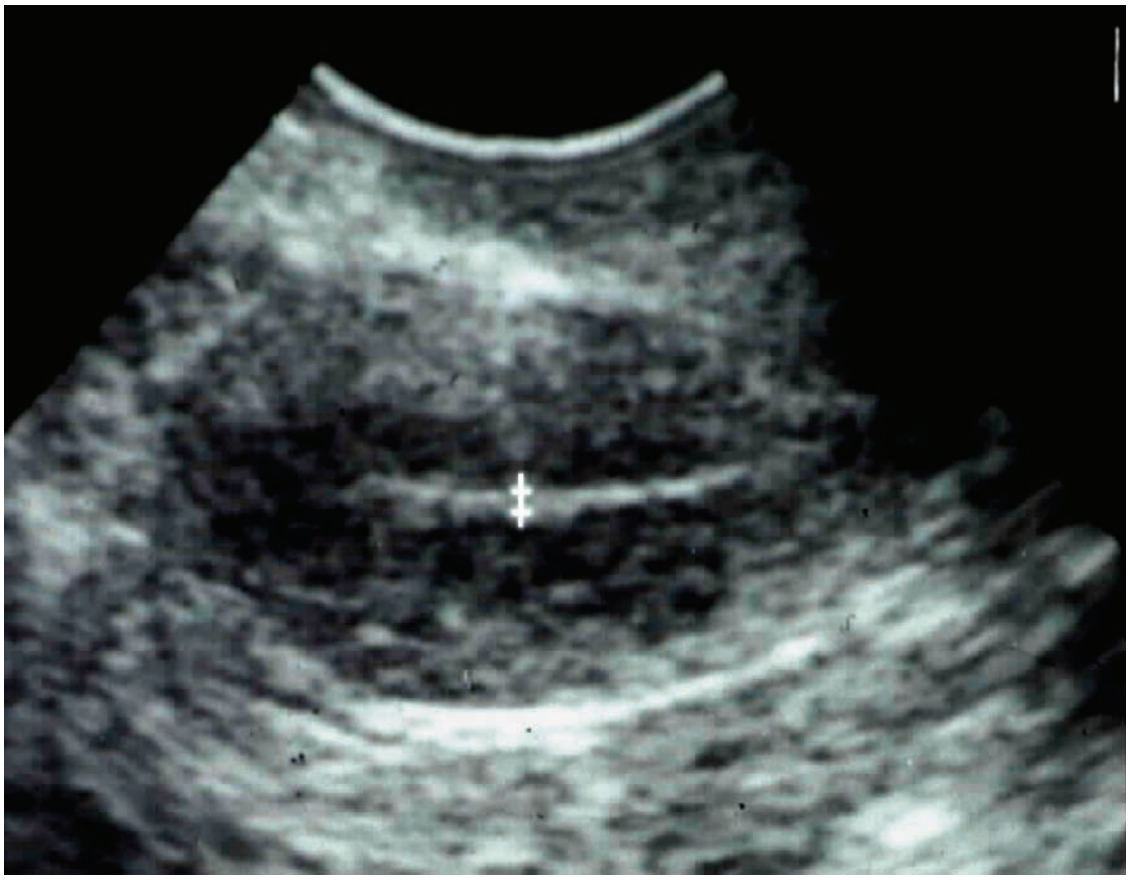

Figure 2. Transvaginal ultrasound of the uterus in the longitudinal plane. *Cursors,* endometrium (in mm) at the thickest point between the two basal layers on the anterior and posterior uterine walls.

examiners at Magee Women's Hospital, one of four facilities managed by the Pittsburgh PLCO Screening Center, routinely measured and recorded endometrial thickness. Therefore, the study group excluded 701 women with transvaginal ultrasound not done by examiners at the Magee Women's Hospital (Fig. 1). Finally, an endometrial thickness measurement from the initial or baseline screening transvaginal ultrasound examination could not be retrieved from medical records in 315 instances. Therefore, the study group for analysis included 1,271 women with known endometrial thickness from a baseline screening transvaginal ultrasound examination.

Data Collection. A self-administered baseline questionnaire completed before ultrasound screening provided information on sociodemographic characteristics (age, race, marital status, and education), body weight and height, reproductive and obstetric history, family history of cancer, personal medical history, cigarette smoking, and use of hormone replacement therapy (HRT). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Two investigators independently abstracted electronic medical records and recorded identical values for endometrial thickness in 97.9% of instances. Discrepant results were resolved by re-review of the medical record.

Endometrial Thickness Measurements. Real-time ultrasonography was done with a 5 MHz vaginal transducer. The vaginal probe was covered with a coupling gel and inserted into a condom, which was coated with gel and inserted into the vaginal fornix, with the subject in the lithotomy position. With the uterus imaged in the longitudinal plan, endometrial thickness was measured at the thickest point between the two basal layers on the anterior and posterior uterine walls (Fig. 2). Endometrial thickness, measured to the nearest millimeters, included both endometrial layers together. Six ultrasound technicians did 98% of all examinations. One of two board-certified obstetrics-gynecology physicians (J.M. and L.M.H.) reviewed printed images from each screening transvaginal ultrasound examination and dictated results, including endometrial thickness measurements, into the medical record. Technician and physician examiners were blind to baseline questionnaire data. Independently of the PLCO study protocol and in a manner consistent with local examination procedures, ultrasound technicians obtained directly from study participants information regarding recent HRT use.

Statistical Methods. Because endometrial thickness measurements were not normally distributed, differences among groups were analyzed by nonparametric means

(Mann-Whitney and Kruskal-Wallis). $P < 0.05$ was considered to be statistically significant. To evaluate the effects of multiple factors simultaneously, multiple variable analysis was done to investigate all factors possibly associated with endometrial thickness. All endometrial thickness measurements were logarithmically transformed in the multiple variable analysis. ANOVA was used in a backward stepwise fashion to identify significant factors while controlling for other covariates. All analyses were done with the SPSS statistical software package (version 11.0). In all models, age, parity, ethnicity, education level, marital status, age at menopause, age at menarche, cigarette smoking, duration since menopause, HRT use, and BMI were treated as polychotomous variables. Use of oral contraceptives, history of fibroids, hypertension, and diabetes were treated as dichotomous variables. BMI was grouped into quartiles (<23.3, 23.4–26.9, 27.0–29.6, and ≥29.7 kg/m^2).

Results

Tables 1, 2, and 3 show the distribution of demographic, reproductive, and other factors for all women and women stratified according to current HRT use. Subjects (n = 1,271) were women with mean age of 62.3 years (range 55–74 years, SD 5.5 years), 70.3% married, 94.9% white, 70.0% educated beyond high school, and 36.5% current HRT users. Endometrial thickness measurements ranged from 1 to 32 mm (median 3 mm, mean 3.97 mm, SD 2.85 mm).

Factors associated with increased endometrial thickness included lower age (P = 0.03), unmarried status (P = 0.01), history of uterine fibroid (P = 0.001), current HRT use ($P < 0.0001$), fewer years since menopause ($P < 0.0001$), history of hypertension (P = 0.04), and increased BMI ($P < 0.0001$). In general, these associations persisted among women not currently using HRT but not among women currently using HRT. Endometrial thickness was not associated with number of live births, family history of breast cancer, or personal history of coronary artery disease, endometriosis, benign breast disease, or infertility (data not shown).

In a final multiple variable analysis including HRT, BMI, history of uterine fibroids, and history of hypertension (R^2 = 0.08), current HRT use ($P < 0.0001$) and increased BMI ($P < 0.0001$) remained as statistically significant factors associated with increased endometrial thickness. History of uterine fibroids (P = 0.051) and history of hypertension (P = 0.058) achieved borderline levels of statistical significance.

Discussion

Studies of premenopausal (6) and postmenopausal (7) women have correlated serum estradiol levels with increased endometrial thickness. To validate transvaginal ultrasound measurement of endometrial thickness as a surrogate marker of estrogen status, we examined the association between endometrial thickness and other factors, including some factors known to be associated with estrogen status in postmenopausal women. In postmenopausal women undergoing screening transvaginal ultrasound for early detection of ovarian cancer, we observed a strong and consistent association between endometrial thickness and factors reflecting exogenous (current HRT use) and endogenous (BMI) estrogen exposure. Other studies have described similar associations involving endometrial thickness, HRT use, and BMI (7-11). In postmenopausal women not receiving HRT, serum estrogen concentrations increase with body weight (12) due to peripheral aromatization of ovarian and adrenal androgens in adipose tissue (13, 14). In women using HRT, serum estradiol levels depend

Table 1. Prevalence of increased endometrial thickness according to sociodemographic characteristics

Characteristics	All subjects (n = 1,271)			Not current HRT users (n = 801)			Current HRT users (n = 461)		
	n	ET ≥3 mm (%)	P	n	ET ≥3 mm (%)	P	n	ET ≥3 mm (%)	P
Age, y									
55–59	498	71.7	0.03	235	61.7	0.78	261	80.5	0.17
60–64	357	66.9		225	55.6		128	88.3	
65–69	266	62.8		213	57.3		52	84.6	
70–74	150	58.7		128	56.3		20	70.0	
Marital status									
Married	893	69.0	0.01	541	60.1	0.04	346	83.2	0.99
Unmarried	378	62.2		260	53.5		115	80.9	
Education									
Less than high school	34	52.9	0.16	30	53.3	0.73	3	66.7	0.23
High school graduate	347	64.8		259	58.3		84	84.5	
Beyond high school	423	66.9		271	57.6		149	83.2	
College graduate	467	69.6		241	58.5		225	81.8	
Ethnicity									
White	1,207	66.6	0.17	756	57.3	0.08	443	82.6	0.60
Black	57	75.4		42	71.4		14	85.7	
Other	7	57.1		3	33.3		4	75.0	

NOTE: P indicates the statistical significance of differences in endometrial thickness (in mm), according to sociodemographic characteristics, for all women, women not currently using HRT, and women currently using HRT. Status with respect to current HRT use was missing in nine instances. ET, endometrial thickness.

Table 2. Prevalence of increased endometrial thickness according to reproductive and gynecologic history

Characteristics	All subjects (n = 1,271)			Not current HRT users (n = 801)			Current HRT users (n = 461)		
	n	ET ≥3 mm (%)	P	n	ET ≥3 mm (%)	P	n	ET ≥3 mm (%)	P
Parity									
Nulliparous	103	69.9	0.42	63	60.3	0.44	39	84.6	0.91
Parous	1,161	66.8		733	57.8		420	82.6	
Unknown	7	42.9		5	40.0		2	50	
Age at menarche, y									
<12	238	71.0	0.75	142	66.2	0.13	94	78.7	0.14
12–13	713	65.2		465	55.7		244	82.8	
≥14	320	67.8		194	57.2		123	85.4	
Age at menopause, y									
<40	14	68.4	0.06	15	66.7	0.086	3	66.7	0.43
40–49	423	60.3		277	50.9		144	78.5	
≥50	819	70.2		506	61.7		307	84.4	
	*10			*3			*7		
Uterine fibroid									
Ever	176	76.1	0.001	93	67.7	0.009	83	85.5	0.56
Never	1,094	65.4		708	56.6		377	82.0	
	*1						*1		
Oral contraceptive use									
Ever	705	65.0	0.22	505	58.6	0.60	191	81.7	0.29
Never	566	69.4		296	56.8		270	83.3	
HRT use									
Never	585	57.8	<0.0001	585	57.8		0		
Former	216	58.3		216	58.3		0		
Current	461	82.6		0			461	82.6	
	*9								
Years since menopause									
<5	278	79.1	<0.0001	131	72.5	0.045	147	85.0	0.64
5–9	322	68.6		162	55.6		157	82.8	
10–14	286	62.9		198	55.6		85	78.8	
≥15	375	59.2		307			65		
	*10			*3			*7		

NOTE: P indicates the statistical significance of differences in endometrial thickness (in mm), according to reproductive and gynecologic history, for all women, women not currently using HRT, and women currently using HRT. Status with respect to current HRT use was missing in nine instances. ET, endometrial thickness; *, missing.

primarily on estrogen type, dose, and manner of administration (15). This background provides a biological explanation for the association between BMI and endometrial thickness observed among non-HRT users and not observed among HRT users (Table 3).

Likewise, other sources of information support associations involving endometrial thickness, age, uterine fibroids, hypertension, and diabetes. Decreasing endometrial thickness with increasing age (Table 1) and increasing duration since menopause (Table 2) may reflect age- and menopause-related declines in ovarian function and blood estrogen levels. Like endometrium, uterine fibroids may contain estrogen and progesterone receptors (16). Epidemiologic studies of uterine fibroids consistently show an association with reproductive history and higher BMI, thereby providing indirect evidence for estrogenic stimulation with respect to the etiology of uterine fibroids (17-19). Recently, Gull et al. (20) reported an association between uterine fibroids and increased endometrial thickness. Hypertension and diabetes are endometrial cancer risk factors (21-23). Obesity, especially central obesity, contributes to lower blood sex hormone binding globulin levels, insulin resistance, diabetes, and high blood pressure (24, 25). A shared association with obesity and altered estrogen status explains, at least in part, the apparent effect of history of hypertension and diabetes on increased endometrial thickness.

Some unexplained variability across women with respect to endometrial thickness may be due to lack of information with respect to type or dose of HRT. For example, continuous and cyclic combination HRT affect endometrial thickness differently (26). Timing of ultrasound in women taking cyclic combination HRT might be expected to affect endometrial thickness measurements as well. For example, women using cyclic HRT achieve maximum endometrial thickness on cycle days 13 to 23 and minimum endometrial thickness immediately after withdrawal bleeding. In addition, women using cyclic HRT typically attain a thicker endometrium than women using continuous HRT (26, 27).

Because our baseline questionnaire lacked items pertaining to uterine bleeding or other gynecologic symptoms, our study group may include some women with uterine symptoms or women with preclinical endometrial disease. Introducing another potential

Table 3. Prevalence of increased endometrial thickness according to other miscellaneous factors

Characteristics	All (n = 1,271)			Non HRT users (n = 801)			HRT users (n = 461)		
	n	ET ≥3 mm (%)	P	n	ET ≥3 mm (%)	P	n	ET ≥3 mm (%)	P
Smoking									
Never	639	68.1	0.57	412	60.4	0.27	220	81.8	0.93
Former	488	66.2		294	55.4		192	83.3	
Current	144	64.6		95	54.7		49	83.7	
Diabetes									
Ever	60	70.0	0.21	41	68.3	0.006	18	72.2	0.037
Never	1,211	66.8		760	57.4		443	83.1	
Hypertension									
Ever	338	69.8	0.04	227	64.3	0.009	108	82.4	0.24
Never	932	65.9		573	55.3		353	82.7	
		*1		*1					
BMI (kg/m^2)									
<23.25	317	55.2	<0.0001	186	43.5	<0.0001	128	72.7	0.26
23.26–26.03	319	66.1		189	54.5		130	83.1	
26.04–29.88	317	69.7		208	59.6		107	88.8	
>29.89	317	76.7		218	71.6		95	88.4	
		*1					*1		

NOTE: P indicates the statistical significance of differences in endometrial thickness (in mm), according to other miscellaneous factors, for all women, women not currently using HRT, and women currently using HRT. Status with respect to current HRT use was missing in nine instances. ET, endometrial thickness; *, missing.

source of unwanted variability, conditions associated with postmenopausal vaginal bleeding, such as endometrial atrophy, polyp, and hyperplasia, might decrease or increase endometrial thickness. Regardless of acute uterine symptoms, however, our study recruitment procedures sought community-dwelling volunteers for a colorectal, ovary, and lung cancer screening study. Unlike groups of women visiting gynecologists or receiving diagnostic ultrasound for evaluation of gynecologic symptoms, our study group is probably not enriched with women manifesting clinically recognizable endometrial abnormalities.

In studies of women with postmenopausal bleeding and often endometrial hyperplasia, ultrasound measurements of endometrial thickness seem reproducible, with intraobserver variation usually <5% and interobserver variation ranging from 5% to 16% (28-31). A large interobserver variation, relative to intraobserver variation, suggests that operator skill and experience may affect the ultrasound measurement of endometrial thickness. In contrast, fewer studies have evaluated the reproducibility of transvaginal ultrasound measurements of endometrial thickness in asymptomatic postmenopausal women, who have, on average, atrophic endometria. In our study population, the median endometrial thickness was 3 mm, well below the 5 mm cutoff usually used in some clinical studies to select women for endometrial sampling (1, 2). Our use of the median endometrial thickness cut point (≥3 mm) corresponds more closely to the somewhat more stringent criterion of ≥4 mm, recently proposed as a cutoff for an abnormally thickened postmenopausal endometrium (32).

In some cases, the sonographic appearance of a thick endometrium may correspond not to a true thickening of the endometrial lining but rather to the unrecognized formation of endometrial polyps or accumulation of fluid within the endometrial cavity. Although technically difficult, our examiners tried to exclude endometrial polyps and fluid accumulations from the endometrial thickness measurement. Still, in some cases, unrecognized polyps or fluid accumulations may have produced falsely elevated endometrial thickness measurements. In clinical practice, the endometrial thickness measurement may be used to monitor women on HRT (33), to evaluate women with postmenopausal bleeding (32), and to select women for more definitive diagnostic procedures, such as dilation and curettage, hysteroscopy, or endometrial biopsy. These latter procedures, in turn, constitute the gold standards for measuring endometrial thickness and recognizing pathologic states involving the endometrium. Recognizing these limitations, future applications using transvaginal ultrasound endometrial thickness measurements as a potential estrogen-related biomarker should consider the role of these more definitive diagnostic procedures in women with increased endometrial thickness.

Our analyses used self-reported height and weight to calculate BMI. Persons tend to underreport weight (34). The tendency to underreport weight should not bias the association between BMI and endometrial thickness, unless women with thinner endometrium tend systematically to underreport weight more so than women with thicker endometrium.

Subjects completed the baseline questionnaires before transvaginal ultrasound. Therefore, results from transvaginal ultrasound could not have biased self-reports of HRT use. Technician and physician examiners were blind to baseline questionnaire data. However, ultrasound technicians typically solicited information regarding recent HRT use directly from study participants (see Methods). Therefore, knowledge of HRT exposures may have biased determinations of endometrial thickness.

Using information prospectively collected on a large sample of postmenopausal women recruited from the general community, we observed consistent and

biologically plausible associations involving various risk factors and a single transvaginal ultrasound measurement of endometrial thickness. These findings validate, at least in part, transvaginal ultrasound as a measurement tool and justify subsequent study of the relationship between endometrial thickness and risk for estrogen-related cancer, including breast cancer. Additional justification for such an approach derives from the independent effects observed on breast cancer risk from increased bone mineral density (35, 36) (another estrogen-related measurement) and increased serum estrogen levels (37).

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