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Endometrial thickness and risk of breast and endometrial carcinomas in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

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Abstract

Postmenopausal women with higher circulating estrogen levels are at increased risk of developing breast and endometrial carcinomas. In the endometrium, excess estrogen relative to progesterone produces a net proliferative stimulus, which may result in endometrial thickening. Therefore, we tested the hypothesis that endometrial thickness is a biological marker of excess estrogen stimulation that is associated with risk of breast and endometrial carcinomas. Endometrial thickness was measured in 1,272 postmenopausal women aged 55–74, who underwent transvaginal ultrasound (TVU) screening as part of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Serial endometrial thickness measurements were available for a subset of women at one (n=1,018), two (n=869) and three years (n=641) after baseline. We evaluated associations between endometrial thickness and breast (n=91) and endometrial (n=14) carcinoma by estimating relative risks (RRs) and 95% confidence intervals (CI) using Cox proportional hazards regression with age as the time metric. Models incorporating baseline endometrial thickness and as a time-varying covariate using all measurements were examined. Median follow-up among study participants was 12.5 years (range: 0.3–13.8 years). Compared to baseline endometrial thickness of 1.0 – 2.99 mm, women with baseline endometrial thickness greater than or equal to 5.0 mm had an increased risk of breast (RR: 2.00, 95% CI 1.15, 3.48) and endometrial (RR: 5.02, 95% CI 0.96, 26.36) carcinomas in models adjusted for menopausal

hormone use and BMI. Our data suggest that increased endometrial thickness as assessed by TVU was associated with increased risk of breast and endometrial carcinomas.

Keywords

transvaginal ultrasound; screening; etiology

INTRODUCTION

Hormones play a critical role in the physiological function of the breast and gynecological organs; however, excess cumulative exposure to hormones or relative imbalances in levels among them may contribute to carcinogenesis at these sites. This view is supported by evidence that hormones represent likely mediators of the effects of breast and endometrial carcinoma risk factors, notably obesity and menopausal hormone replacement, and that elevated circulating levels of estrogens and androgens increase risk of these carcinomas among postmenopausal women^{1,2}. Nonetheless, the magnitude of risk associated with these factors would seem too low to fully account for the pathogenesis of these tumors. Therefore, these risk factors may represent imperfect surrogates for the biological effects of hormones and other carcinogenic influences on these tissues. Thus, investigations to identify additional markers of risk are warranted.

Previous research suggests that endometrial thickness, as measured by transvaginal ultrasound (TVU), is a potential biomarker of imbalances such as the proliferative effects of estrogens, the opposing differentiating influences of progesterone, and possibly other pro- and anti-carcinogenic factors. Consistent with this interpretation, an analysis in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial demonstrated that factors associated with higher levels of growth promoting factors such as younger age, higher BMI, presence of uterine fibroids, current menopausal hormonal use, fewer years since menopause, and history of diabetes or hypertension were associated with a thicker endometrium³. Other cross-sectional studies confirm these associations and provide additional evidence that insulin resistance and polycystic ovary syndrome are directly associated with thicker endometrial measurements⁴⁻⁸. Furthermore, in a cross-sectional study serum estradiol and estrone levels were significantly higher in women with endometrial thickness greater than or equal to 5 millimeters compared to women with endometrial thickness below this threshold, although no difference in circulating progesterone levels was observed⁹.

TVU is often performed to clinically investigate the source of gynecological signs or symptoms and has recently been evaluated as a method of ovarian cancer screening^{9,10}. Data demonstrate that endometrial thickening as assessed by TVU is a useful diagnostic test for identifying prevalent endometrial carcinoma or its precursors both among women investigated for symptoms and among asymptomatic participants in an ovarian cancer screening trial¹¹. However, the relationship of endometrial thickness among asymptomatic women and risk of incident breast and endometrial carcinomas has not been evaluated in a prospective study. Accordingly, we assess the hypothesis that pre-diagnostic measurement of

endometrial thickness by TVU among postmenopausal women in the PLCO Cancer Screening Trial is associated with breast and endometrial carcinoma risk.

MATERIAL AND METHODS

Study population

The PLCO Cancer Screening trial is a National Cancer Institute sponsored clinical trial designed to test the effectiveness of screening tests to reduce mortality from prostate, lung, colorectal and ovarian cancer¹². Our study included women enrolled at the University of Pittsburgh PLCO Screening Center between November, 1993 and November, 2000 who were randomized to the screening arm of the trial. TVUs and blood tests for cancer antigen (CA)-125 were performed annually for female participants in the screening arm⁹.

The inclusion criteria of our study population have been previously reported³. Briefly, of 4,228 women enrolled in the Pittsburgh PLCO Screening Center, 2,696 women had intact uteri and ovaries and were therefore eligible for TVU screening. Although PLCO did not record endometrial thickness as part of the ovarian cancer screening, examiners at Magee Women's Hospital, one of four Pittsburgh PLCO Screening Centers, routinely measured and recorded endometrial thickness. Therefore, this was the only PLCO Screening Center included in our study. Our final sample of 1,272 women includes all women with a known endometrial thickness from the baseline screening TVU examination performed by examiners at Magee Women's Hospital. This study was approved by the University of Pittsburgh Institutional Review Board.

Data collection

Participants completed a self-administered questionnaire detailing age, race/ethnicity, education, marital status, anthropometric measures (weight and height), menstrual and reproductive characteristics (age at menarche, age at menopause, parity), menopausal hormone use, oral contraceptive use, smoking history, history of diabetes, hypertension, uterine fibroids, and family history of cancer. Incident diagnoses of breast and endometrial carcinomas that occurred during the follow-up period (baseline screening - earliest of carcinoma incidence or death - 13 years of follow-up, or December 31, 2009) were ascertained through self-report and confirmed by medical chart and death certificate review. Information on hysterectomy status during follow-up was not available. Forty-eight women reported a prior breast cancer diagnosis at baseline and were not included in the incident breast carcinoma analyses; however, these women were included in analyses of endometrial carcinoma risk.

Endometrial thickness measurements

The measurement of endometrial thickness in this subcohort has been previously described³. Briefly, real-time ultrasonography was performed using a 5 MHz vaginal transducer. The vaginal probe was inserted into the vagina with the subject in the lithotomy position. Endometrial thickness, measured to the nearest millimeter, was measured at the thickest point between the two basal layers on the anterior and posterior uterine walls and included both endometrial layers together. Six ultrasound technicians performed 98% of all

examinations. One of two board-certified obstetrics-gynecology physicians (JM and LMH) reviewed images from each screening TVU examination and dictated results, including endometrial thickness measurements, into the medical record. Technician and physician examiners were blind to baseline questionnaire data.

Statistical methods

Cox proportional hazard models were used to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs) for the association between endometrial thickness and risk of breast and endometrial carcinoma. The proportional hazards assumption was tested using Schoenfeld's global test. Age was used as the underlying time-metric in all analyses. Follow-up time began at the age a woman had the baseline TVU and ended at age of breast or endometrial carcinoma diagnosis or censoring related to death or end of follow-up. We modeled the association between endometrial thickness and carcinoma risk in two ways: using only the baseline measure and as a time-varying covariate using all the measurements. In the time-varying covariate analysis we let endometrial thickness values change at year one, two or three if measurements were available, thus modeling endometrial thickness at the last available TVU. Serial endometrial thickness measurements were available for a subset of women at one (n=1,018), two (n=869) and three years (n=641) after baseline. As the number of women with endometrial thickness measures declined at each year, we evaluated associations between the number of endometrial thickness measures and personal characteristics among the non-cases using chi-square tests.

Endometrial thickness was categorized into three groups: 1.0 – 2.99, 3.0 – 4.99 and ≥ 5.0 mm. Clinicians vary in their referral of symptomatic women for further investigations; however, cut-offs between 3.0 and 5.0 mm are typically used¹³. Endometrial thickness between 1.0 and 2.99 mm was the reference category in all models. Tests for linear trend across the endometrial thickness categories were calculated by including an ordinal form of endometrial thickness (0, 1, 2) in the models. BMI and menopausal hormone use were included as adjustment factors given their significant association with endometrial thickness in the previous PLCO analysis and their known association with both breast and endometrial carcinoma risk³. We performed additional adjustments for variables that were not significantly associated with endometrial thickness in the previous analysis, including parity, oral contraceptive use and age at menopause; however, these factors did not affect associations of endometrial thickness and carcinoma risk. Therefore, final analyses adjusted for BMI and menopausal hormone use only. We also examined associations between hormonal and reproductive factors, breast, and endometrial carcinoma risk in Cox proportional hazard models unadjusted and adjusted for endometrial thickness.

In addition, we conducted several sensitivity analyses: 1.) breast and endometrial carcinoma models were restricted to never and former users of menopausal hormones, 2.) breast carcinoma models were defined by estrogen receptor (ER) status (negative vs. positive), and 3.) breast carcinoma models were stratified by parity (nulliparous vs. parous) and number of years since baseline (baseline to 5 years vs. 5–10 years after baseline). The last model was conducted to assess whether endometrial thickness was differentially associated with risk in the interval between baseline and 5 years after baseline and in the interval from 5 to 10 years

after baseline. All tests of statistical significance were two-sided. All statistical analyses were performed using the SAS Software Package, version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the study population are shown in Table 1. Age at study enrollment, age at menopause, menopausal hormone use and BMI were significantly associated with endometrial thickness ($p < 0.05$). Older women were more likely to have a thinner endometrium, while younger women were more likely to have a thicker endometrium. Older age at menopause, current menopausal hormone use, and obesity were associated with endometrial thickness measures greater than 5.0 mm. Median baseline endometrial thickness significantly differed between endometrial carcinoma cases (4.5 mm), breast carcinoma cases (4.0 mm) and women who did not develop either carcinoma during follow-up (3.0 mm, Kruskal-Wallis $p = 0.003$, Table 2).

We examined associations between baseline endometrial thickness and risk of breast and endometrial carcinomas (Table 3). Compared to baseline endometrial thickness of 1.0 – 2.99 mm, women with baseline endometrial thickness between 3.0 – 4.99 mm did not have increased risks of either breast (RR: 0.92, 95% CI 0.57, 1.71, $p = 0.97$) or endometrial (RR: 1.84, 95% CI 0.35, 9.79, $p = 0.47$) carcinomas. Baseline endometrial thickness greater than or equal to 5.0 mm was significantly associated with breast (RR: 2.00, 95% CI 1.15, 3.48, $p = 0.01$) and endometrial (RR: 5.02, 95% CI 0.96, 26.36, $p = 0.06$) carcinoma risk compared to the reference category of 1.0 – 2.99 mm. A significant trend of increasing endometrial thickness and carcinoma risk was observed for both breast ($p_{\text{trend}} = 0.01$) and endometrial carcinomas ($p_{\text{trend}} = 0.04$). In analyses restricted to never and former users of menopausal hormones, associations between baseline endometrial thickness greater than or equal to 5.0 mm relative to endometrial thickness 1.0–2.99 mm were similar to the main results of both outcomes. In breast carcinoma models defined by ER status, significant associations for ER negative ($n = 12$, RR: 1.34, 95% CI 0.30, 6.12, $p = 0.87$) and ER positive ($n = 61$, RR 1.68, 95% CI 0.86, 3.29, $p = 0.13$) tumors were not observed for endometrial thickness greater than or equal to 5.0 mm compared to the referent. In models stratified by parity, endometrial thickness greater than or equal to 5.0 mm was significantly associated with breast carcinoma risk among parous (RR: 2.34, 95% CI 1.27, 4.34) but not nulliparous women (RR: 1.19, 95% CI 0.65, 2.19, $p_{\text{interaction}} = 0.26$). We did not observe significant associations between risk factors and breast or endometrial carcinoma risk in models unadjusted and adjusted for endometrial thickness (Supplementary Table 1).

Endometrial thickness modeled as a time-varying covariate was not significantly associated with either breast or endometrial carcinoma risk (Table 4). In evaluating characteristics associated with the number of endometrial thickness measures among the non-cases, age and parity were significantly associated, such that younger women had fewer endometrial thickness measures while parous women had a higher number endometrial thickness measures compared to nulliparous women. We ran time-varying models stratified by parity and did not observe significant associations between endometrial thickness and breast or endometrial carcinoma risk in these models. To assess whether endometrial thickness

showed different associations over the follow-up period, we compared breast carcinoma risk within the first 5 years after baseline to breast carcinoma risk in the interval 5–10 years after baseline. Within the first 5 years of follow-up, endometrial thickness greater than or equal to 5 mm was significantly associated with breast carcinoma risk (RR: 2.77, 95% CI 1.19, 6.47, $p=0.02$) whereas the effect was attenuated in the interval 5 to 10 years after baseline (RR: 1.55, 95% CI 0.74, 3.23, $p=0.24$). Although risk was stronger within the first five years of baseline, these two relative risks were not significantly different ($p=0.53$).

DISCUSSION

This is the first prospective study to examine relationships between endometrial thickness and risk of incident breast or endometrial carcinomas. Compared to endometrial thickness between 1.0 and 2.99 mm, endometrial thickness of 5.0 mm or greater was associated with a two-fold risk of developing breast carcinoma and a five-fold risk of developing endometrial carcinoma. Additionally, among never and former hormone users, associations between endometrial thickness and breast and endometrial carcinoma risk were similar to the main results, although attenuated due to reduced numbers of cases. In the presence of other hormonally-related risk factors, including obesity and menopausal hormone use, endometrial thickness was a significant predictor of these carcinomas, suggesting that endometrial thickness adds additional risk information. Furthermore, a dose-response relationship was observed for increasing endometrial thickness and endometrial cancer risk whereas a threshold effect was noted for breast cancer risk.

In modeling endometrial thickness as a time-varying covariate we allowed endometrial thickness to change each time a TVU was performed. This approach produced weaker associations between endometrial thickness and carcinoma risk compared to models using the baseline measure. One potential explanation is that the subset of women with multiple endometrial thickness measures was different than the women contributing data to the baseline analysis. Duration and parity were associated with the number of endometrial thickness measures in our study. Age was used as the time metric in all analyses and when models were adjusted for or stratified by parity, results were consistent. We also assessed risks of developing breast carcinoma in the interval from baseline to 5 years and in the interval between 5 and 10 years after baseline. We observed a somewhat stronger relative risk for endometrial thickness within the first 5 years after baseline, suggesting that the effect endometrial thickness on breast carcinoma risk might diminish with time.

Using the same study population, a previous investigation explored determinants of thicker endometrium, which included obesity and current use of menopausal hormones, factors also related to increased risks of breast and endometrial carcinomas³. Thus, endometrial thickness may be a useful surrogate of estrogen status in postmenopausal women. One biological mechanism relating obesity and menopausal hormone use to thicker endometrium and cancer risk is through imbalances in estrogen and progesterone¹⁴. In the normal endometrium, the proliferative effects of estrogen are opposed by progesterone, but deficits of progesterone relative to estrogen may result in excessive proliferation of glandular epithelium¹⁵. Increases in cellular proliferation can result in a higher likelihood of mutations in proto-oncogenes and tumor suppressor genes, while impairment of apoptotic

mechanisms may allow cells harboring such mutations to survive and clonally expand, leading to cancer. Importantly, our findings extend the previous cross-sectional study by providing evidence that endometrial thickness is significantly associated with incident breast and endometrial carcinoma risk and that this relationship persists after adjustment for other hormonally-related risk factors, including BMI, menopausal hormone use, parity and oral contraceptive use.

In the setting of postmenopausal bleeding, the Society of Radiologists in Ultrasound recommends that an endometrial thickness of 5.0 mm or greater prompt additional evaluation, such as sonohystero-graphy, office hysteroscopy, or endometrial biopsy¹⁶. This recommendation is based on a meta-analysis of 85 published studies that reported a sensitivity of 96% for endometrial carcinoma detection when a threshold of 5.0 mm is used¹⁷. Conversely, current recommendations for women with asymptomatic endometrial thickening advise against further follow-up, based on a 1% incidence of endometrial carcinoma among this subgroup¹⁸. A recent meta-analysis of studies examining the diagnostic accuracy of endometrial thickness in asymptomatic postmenopausal women reached similar conclusions¹³. Using a threshold of 5.0 mm to indicate an abnormal TVU resulted in highly variable sensitivity and specificity estimates, leading the authors of this study to conclude that endometrial thickness assessed by TVU should not be used as a screening tool in asymptomatic postmenopausal women. In contrast, in a nested case-control study of the United Kingdom Collaborative Trial of Ovarian Cancer Screening, a receiver operating characteristic (ROC) curve analysis identified an endometrial thickness of 4.45 mm as the optimal threshold for endometrial carcinoma detection among asymptomatic women, which is similar to the 5.0 mm cutoff used in symptomatic women¹¹. Although the current literature is equivocal on the role of endometrial thickness in the triage of asymptomatic women, our study of women who are likely to be asymptomatic, provides evidence that an endometrial thickness of 5.0 mm or greater may serve as a useful marker of future breast and endometrial carcinoma risk in this subgroup.

While our study had a number of strengths, including the prospective evaluation of endometrial thickness and subsequent carcinoma risk, information on reproductive and lifestyle risk factors, and systematic follow-up of the screening participants, there were some limitations. First, we lacked information on hysterectomy status during the trial. This could potentially bias our results towards the null if hysterectomies were more likely to occur in women with thicker endometrium. As endometrial thickness is associated with vaginal bleeding, a higher prevalence of hysterectomy among women with a thicker endometrium cannot be ruled out. Furthermore, the low number of breast and endometrial carcinoma cases limited our statistical power. Differences in characteristics of women with multiple TVUs compared to fewer TVUs, possible variation in the classification of endometrial thickness measures within and between gynecologists, and potential inclusion of women with postmenopausal bleeding are additional limitations of our study.

Using prospectively collected information from women enrolled in a screening trial, we observed increased risks of breast and endometrial carcinoma associated with endometrial thickness greater than 5.0 mm, suggesting that endometrial thickness may be a marker of tissue-related changes in hormonal carcinogenesis. Future etiologic studies that include

endometrial thickness measures on a larger number of truly asymptomatic women, examine relationships between endometrial thickness and hormone measures, and explore relationships with various tumor characteristics may contribute additional insights into the hormonal carcinogenesis of breast and endometrial carcinoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Impact Statements

Previous investigations have shown that endometrial thickness is related to obesity and menopausal hormone use, factors associated with a higher incidence of breast and endometrial carcinomas. Given these associations, we investigated if endometrial thickness was independently associated with incident breast or endometrial carcinoma risk. In our cohort of 1,272 women, endometrial thickness greater than 5 millimeters was associated with a two-fold risk of breast carcinoma and a five-fold risk of endometrial carcinoma.

Table 1

Baseline characteristics of the study participants by endometrial thickness

Endometrial thickness (mm)	1.0 – 2.99 n=420	3.0 – 4.99 n=530	≥ 5.0 n=322	p
Age, years				0.02
55–59	141 (33.6)	221 (41.7)	136 (42.2)	
60–64	118 (28.1)	141 (26.6)	99 (30.7)	
65–69	99 (23.6)	107 (20.2)	60 (18.6)	
70–74	62 (14.8)	61 (11.5)	27 (8.4)	
Ethnicity				0.29
White	402 (95.7)	500 (94.3)	296 (91.9)	
Black	14 (3.3)	22 (4.1)	20 (6.2)	
Other	4 (1.0)	8 (1.5)	5 (1.9)	
Parity				0.54
Nulliparous	43 (10.2)	55 (10.4)	38 (11.8)	
Parous	373 (88.8)	474 (89.4)	282 (87.5)	
Age at menarche, years				0.35
<12	69 (16.4)	167 (20.4)	62 (19.2)	
12–13	148 (35.0)	281 (53.0)	184 (57.1)	
≥14	103 (24.5)	141 (26.6)	76 (23.6)	
Age at menopause, years				<0.0001
<40	6 (1.4)	7 (1.3)	6 (1.9)	
40–44	41 (9.8)	55 (10.2)	27 (8.4)	
45–49	127 (30.2)	145 (27.1)	75 (23.3)	
50–54	213 (50.7)	295 (55.5)	150 (46.6)	
>55	25 (5.9)	72 (13.6)	59 (18.2)	
Oral contraceptive use				0.25
Never	247 (58.8)	286 (53.9)	173 (53.7)	
Ever	173 (41.2)	244 (46.0)	149 (46.3)	
Menopausal hormone use				<0.0001
Never	247 (58.8)	239 (45.1)	100 (31.1)	

Endometrial thickness (mm)	1.0 – 2.99 n=420	3.0 – 4.99 n=530 n (%)	≥ 5.0 n=322	p
Current	80 (19.0)	203 (38.5)	178 (55.3)	
Former	90 (21.4)	82 (15.5)	44 (13.7)	
BMI				<0.0001
Normal weight	25 (5.12)	195 (36.8)	115 (35.7)	
Overweight	133 (31.2)	207 (39.1)	155 (48.0)	
Obese	71 (17.1)	128 (24.1)	104 (32.2)	
Smoking status				0.65
Never	20 (4.8)	274 (51.7)	161 (50.0)	
Current	51 (12.1)	62 (11.7)	31 (9.6)	
Former	165 (39.3)	194 (36.6)	130 (40.4)	
Diabetes				0.26
No	403 (95.9)	500 (94.0)	302 (93.8)	
Yes	17 (4.0)	21 (4.0)	20 (6.2)	

chi-square p value

Table 2

Baseline endometrial thickness measurements among women who developed breast or endometrial carcinoma and among women who did not develop these carcinomas during follow-up

	Entire subcohort N=1,272	Breast carcinoma n=91	Endometrial carcinoma n=14	Women without breast or endometrial carcinoma n=1,167
Endometrial thickness (mm)				
1.0 – 2.99	420 (33.0)	24 (26.4)	2 (14.3)	394 (33.8)
3.0 – 4.99	530 (41.7)	31 (34.1)	5 (35.7)	494 (42.3)
≥ 5.0	322 (25.3)	36 (39.6)	7 (50.0)	279 (23.9)
Median (range)	3.0 (1.0–32.0)	4.0 (1.0–19.0)	4.5 (2.0–18.0)	3.6 (1.0–2.0)
Mean (std. dev)	4.0 (2.8)	4.7 (3.5)	5.6 (3.2)	3.9 (2.7)

Data are n (%) unless otherwise indicated

Std. dev.: Standard deviation

Adjusted relative risks (RRs) and 95% confidence intervals (CIs) for breast and endometrial carcinoma risk in relation to baseline endometrial thickness, N=1,272

Table 3

Endometrial thickness (mm)	Breast carcinoma ¹ n=91			Endometrial carcinoma n=14		
	RR (95% CI) ²	p ³	ptrend ⁴	RR (95% CI) ²	p ³	ptrend ⁴
1.0 – 2.99	1.00 (Ref)	0.008	0.01	1.00 (Ref)	0.10	0.04
3.0 – 4.99	0.99 (0.57, 1.71)			1.84 (0.35, 9.79)		
≥ 5.0	2.00 (1.15, 3.48)			5.02 (0.96, 26.36)		

¹ Forty-eight women were excluded from the incident breast cancer analyses due to a prevalent breast cancer at baseline

² RR adjusted for menopausal hormone use and body mass index

³ p³ is a 2 degree of freedom test for the overall effect of endometrial thickness

⁴ ptrend is a 1 degree of freedom test

Table 4

Adjusted relative risks (RRs) and 95% confidence intervals (CIs) for breast and endometrial carcinoma risk in relation to endometrial thickness, as a time-varying covariate, N=1,272

Endometrial thickness (mm)	Breast carcinoma	Endometrial carcinoma
	RR (95% CI) ^f	RR (95% CI) ^f
1.0 – 2.99	1.00 (Ref)	1.00 (Ref)
3.0 – 4.99	1.35 (0.83, 2.21)	1.24 (0.29, 5.36)
≥ 5.0	1.32 (0.73, 2.40)	3.02 (0.71, 12.81)

^f RR adjusted for menopausal hormone use and body mass index