Serial endometrial thickness and risk of non-endometrial hormone-dependent cancers in postmenopausal women in UK Collaborative Trial of Ovarian Cancer Screening

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CONTRIBUTION

What are the novel findings of this work?
This is the first study to investigate the association between endometrial thickness (ET) and the risk of eight non-endometrial hormone-dependent cancers in postmenopausal women, and has greater statistical power than the only prior study that considered breast cancer. A doubling of ET was found to increase significantly the risk of ovarian and lung cancer in addition to breast cancer.

What are the clinical implications of this work?
Clinicians performing transvaginal ultrasonography should be aware that postmenopausal women with high and/or increasing ET are at an increased risk of breast, ovarian and lung cancer.

ABSTRACT

Objective Estrogen is a well-established risk factor for various cancers. It causes endometrial proliferation, which is assessed routinely as endometrial thickness (ET) using transvaginal ultrasound (TVS). Only one previous study, restricted to endometrial and breast cancer, has considered ET and the risk of non-endometrial cancer. The aim of this study was to explore the association between baseline and serial ET measurements and nine non-endometrial hormone-sensitive cancers, in postmenopausal women, using contemporary statistical methodology that attempts to minimize the biases typical of endogenous serial data.

Methods This was a cohort study nested within the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). In the ultrasound arm of UKCTOCS, 50,639 postmenopausal women, aged 50–74, underwent annual TVS examination, of whom 38,105 had a valid ET measurement, no prior hysterectomy and complete covariate data, and were included in this study. All women were followed up through linkage to national cancer registries. The effect of ET on the risk of six estrogen-dependent cancers (breast, ovarian, colorectal, bladder, lung and pancreatic) was assessed using joint models for longitudinal biomarker and time-to-event data, and Cox models were used to assess the association between baseline ET measurement and these six cancers in addition to liver cancer, gastric cancer and non-Hodgkin’s lymphoma (NHL). All models were adjusted for current hormone-replacement therapy (HRT) use, body mass index, age at last menstrual period, parity and history of oral contraceptive pill use.

Results The 38,105 included women had a combined total of 267,567 (median, 8; interquartile range, 5–9) valid ET measurements. During a combined total of 407,838 (median, 10.9) years of follow-up, 1398 breast, 351 endometrial, 381 lung, 495 colorectal, 222 ovarian, 94 pancreatic, 79 bladder, 62 gastric and 38 liver cancers and 52 NHLs were registered. Using joint models, a doubling of ET increased significantly the risk of breast (hazard ratio (HR), 1.21; 95% CI, 1.09–1.36; P = 0.001), ovarian (HR, 1.39; 95% CI, 1.06–1.82; P = 0.018) and lung (HR, 1.25; 95% CI, 1.02–1.54; P = 0.036) cancers. There were
no statistically significant associations between ET and the remaining six cancers.

**Conclusion** Postmenopausal women with high and/or increasing ET on TVS are at increased risk of breast, ovarian and lung cancer. It is important that clinicians are aware of these risks, as TVS is a common investigation.

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**INTRODUCTION**

Cumulative estrogen exposure is linked to many types of cancers, particularly female cancers. In breast and endometrial cancer, and, to a lesser extent, ovarian cancer, this increase in risk associated with higher levels of estrogen is particularly well established. For lung cancer, there is a growing consensus that estrogens contribute to the increased rates seen in women compared with men, and that smoking further augments the effect of estrogen. For colorectal cancer, the evidence is unclear, with an increased risk reported for estrogen with a decreased risk for estrogen. The association between estrogen exposure and risk of gastric, pancreatic and bladder cancer is less clear, but there is some evidence of a decreased risk associated with estrogen. For non-Hodgkin’s lymphoma (NHL), definitive associations with estrogen have not been established.

Estrogen receptors are expressed in many tissues, including the endometrium. Cumulative estrogen exposure, especially in postmenopausal women, leads to endometrial proliferation which could be easily assessed as endometrial thickness (ET) using transvaginal ultrasound (TVS). In postmenopausal women, the adipose tissue provides an additional source of estrogen, which in turn causes proliferation of the endometrium. Whilst increased ET is well-established as an early detection marker for endometrial cancer, ET could also be a potential risk marker for other hormone-sensitive cancers. A prospective study within the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial reported that an ET > 5 mm, compared with an ET < 3 mm, was associated with a 2-fold increase in the risk of breast cancer. This study was limited by sample size (1272 women with 91 breast cancers) and the main analysis was restricted to only the baseline measurement. Furthermore, the statistical method used to incorporate the serial measurements was susceptible to bias.

Using a prospective cohort design in the ultrasound arm of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and a joint model of longitudinal and time-to-event data, the aim of this study was to explore whether ET measurement at baseline, or serial change over 11 years of screening, is associated with the risk of nine estrogen-dependent non-endometrial cancers in postmenopausal women.

**METHODS**

**Participants**

UKCTOCS (ISRCTN22488978; ClinicalTrials.gov NCT00058032) is a multicenter randomized controlled trial of 202638 postmenopausal women aged 50–74 years, from England, Wales and Northern Ireland, randomized to annual screening either using TVS (ultrasound arm; n = 50639) or serum CA125 (multimodal arm; n = 50640) or to no screening (control arm; n = 101359). The eligibility criteria and trial details are described elsewhere. UKCTOCS was approved by the UK North West MREC (00/8/34) on 23rd June 2000. Participants provided written consent for use of their data in secondary studies. This analysis used data from the ultrasound arm, in which women were offered annual TVS screening between 17th April 2001 and 31st December 2011. We limited the analysis to those who had not undergone hysterectomy prior to recruitment, had complete covariate data and had at least one valid ET measurement.

**TVS data**

Women underwent annual TVS scans, with repeat scans performed when abnormal adnexal morphology was noted. Between 2001 and 2008, the scans were performed using a Kretz/Medison SA9900 machine (Medison, Seoul, South Korea), and from 2008 they were performed using a Medison Accuvix XQ machine (Medison). In addition to ovarian morphology, ET measurements were collected routinely and entered in a central web-based trial management system. ET was recorded at the thickest anteroposterior diameter of the endometrium in a sagittal plane of the uterus. Calipers were placed perpendicular to the outer edge of the endometrium. If there was fluid in the endometrial cavity, the cavity fluid and the double endometrial stripe were measured, and the fluid diameter at the same point was subtracted.

**Cancer notification**

All women were flagged with the NHS Digital for England and Wales and Northern Ireland Cancer Registry, and cancer notifications (site, morphology and date of diagnosis) included in this analysis were diagnosed by 31st December 2014. Nine types of cancer that have a possible association with estrogen were identified using cancer registry ICD-10 codes: ovarian (C56, C57, C48), breast (C50), lung (C34), colorectal and anal (C18–C21), pancreatic (C25), bladder (C67), liver (C22), gastric (C16) and NHL (C85).

**Covariate data**

Data on hysterectomy, height, weight, current or past use of the oral contraceptive pill (OCP), parity, current use of hormone-replacement therapy (HRT) and age at last...
menstrual period (LMP) were captured at recruitment. Approximately 77% of women also completed a postal follow-up questionnaire 3–5 years post-randomization, which included additional data on alcohol intake, smoking and hysterectomy. Data on hysterectomy were also obtained from Hospital Episodes Statistics (HES England) by identifying all women with Q07 (abdominal excision of the uterus) and Q08 (vaginal excision of the uterus) records and from the ultrasound scan form, which also recorded current HRT use.

**Statistical analysis**

Of nearly 270,000 ET measurements, 10 values > 50 mm (maximum of 503 mm) were excluded arbitrarily from the analysis. The remaining ET measurements were transformed to the binary logarithmic scale; the calculated hazard ratios (HR) therefore reflect a doubling of ET.

The association between ET and each cancer type was explored using joint models, that modeled simultaneously the two related processes of serial measurements over time (longitudinal submodel) and time to clinical outcome (survival submodel). Modeling either process in isolation may introduce bias due to the endogenous nature of the biomarker. Furthermore, joint models use best unbiased linear predictions of the underlying biomarker process in the survival submodel, smoothing out some of the potential measurement error. This can increase the signal and further reduce bias (Appendix S1).

For the longitudinal submodel, current use of HRT at baseline and at each ET measurement, age at LMP, body mass index (BMI), parity and OCP use were included as fixed effects, in addition to a subject-specific random intercept. The survival submodel included the same adjustment covariates, as well as the association parameter that links the two submodels. We specified the current value link, which is the fitted value including random effects from the longitudinal submodel. The baseline hazard was modeled using a Weibull distribution for all cancers except breast cancer, which used a cubic spline model with one interior knot. Further details of the joint model are given in Appendix S1.

Both longitudinal and survival submodels used age as the time metric, implying delayed entry for the survival analysis. Analysis time was defined as from age at first ET measurement to age at cancer diagnosis of interest. Censorship was age at 31st December 2014, or earlier if there was poststudy-entry hysterectomy or death. There was no censorship for diagnosis of any other cancer prior to diagnosis of the cancer of interest, nor were they treated as a competing risk. A lung cancer-specific sensitivity analysis included alcohol and smoking as covariates for both submodels, reducing the sample size by 33%. The joint model failed to converge for the three rarest cancers (NHL, gastric and liver). For comparison, the association between ET and each cancer based on only the baseline measurement was assessed using a Cox model for all nine cancers. The proportional hazards assumption was assessed using the Schoenfeld residuals.

In addition, a standalone longitudinal mixed model, restricted to ET measurements in women with none of the nine investigated cancers or endometrial cancer, was used to construct age-dependent reference curves at various centiles for normal ET measurements. All statistical analyses were performed using Stata 15.1 (StataCorp. LLC, College Station, TX, USA) and the joint models were fitted using the user-written command `stjm`. Hazard functions with 95% CI were estimated for ET values of 2.5 mm and 5 mm (the ratio of which being equivalent to the HR for the log2 ET measurements) and presented graphically for the age range, 50–80 years. One-, 5- and 10-year absolute risk estimates were calculated for selected cancers, ET measurements and ages.

**RESULTS**

Of 50,639 women randomized to the ultrasound arm in UKCTOCS, 9651 had undergone hysterectomy prior to recruitment and 237 underwent hysterectomy between recruitment and the first scan. A further 1893 women had no ET measurements and 753 (1.9%) women had missing data on at least one of the included covariates. The analysis therefore included 38,105 women who had at least one ET measurement and complete data on covariates (Figure 1). Overall, there were 267,567 (36,169 baseline, 231,398 serial) ET measurements, with a median of 8 (interquartile range (IQR), 5–9; maximum, 19) per participant.

At recruitment, the median age of the women was 60.6 (IQR, 56.2–66.2) years, median BMI was 25.6 (IQR, 23.2–28.9) kg/m², median age at LMP was 50.6 (IQR, 47.9–53.1) years and 17.4% of women were currently using HRT. Of the women, 88.0% were parous and 60.4% had used OCP.

Table 1 shows the baseline and follow-up characteristics in the 36,168 women with an ET measurement at baseline, overall and according to baseline ET. Baseline ET was < 3 mm in 18,429 (51.0%) women, ≥ 3 to < 5 mm in 11,694 (32.3%) women and ≥ 5 mm in 6,045 (16.7%) women. All factors were strongly associated (P < 0.0001) with ET, except for smoking (P = 0.254) and OCP use (P = 0.021). Age and alcohol use were associated negatively with ET, whereas age at LMP, BMI, parity, HRT use and OCP use were associated positively with ET. Figure 2 depicts the age-dependent reference curves for estimated ET in women who did not develop any of the described cancers (n = 35,058), based on a standalone mixed model. Median ET was estimated to be 2.91 mm in women at age 50 years, with the endometrium thinning slightly over time to 2.46 mm at age 80.

During a combined total of 407,838 (median, 10.9; IQR, 9.8–11.8) years of follow-up, 1,398 breast, 381 lung, 495 colorectal, 222 ovarian, 94 pancreatic, 79 bladder, 62 gastric and 38 liver cancers and 52 NHLs were registered. For the joint models, there was a slight difference in sample size between the analyses for each cancer type, which was due to the cancer of interest occurring between recruitment and first ET measurement in some cases. The
Postmenopausal women randomized to ultrasound arm of UKCTOCS ($n=50639$)

Excluded:
- Hysterectomy prior to recruitment ($n=9651$)
- Hystereotomy between recruitment and first scan ($n=237$)

No prior hysterectomy ($n=40751$)

No valid ET measurement ($n=1893$)

At least one ET measurement ($n=38858$)

Data missing for at least one covariate* ($n=753$)

At least one ET measurement and no missing data† ($n=38105$)

Diagnosis‡
- Breast cancer ($n=1398$)
- Ovarian cancer ($n=222$)
- Colorectal cancer ($n=495$)
- Lung cancer ($n=381$)
- Pancreatic cancer ($n=94$)
- Bladder cancer ($n=79$)
- Gastric cancer ($n=62$)
- Liver cancer ($n=38$)
- NHL ($n=52$)
- Endometrial cancer ($n=351$)
- The above-mentioned cancer ($n=35058$)

**Figure 1** Flow diagram summarizing inclusion of study population.

*Body mass index, age at scan, age at menopause, oral contraceptive pill, current hormone-replacement therapy, parity. †Final cohort. ‡Some women had more than one cancer diagnosis. ET, endometrial thickness; NHL, non-Hodgkin’s lymphoma; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening.

sample size in the six successfully fitted joint models varied from 38,078 (breast cancer) to 38,105 (ovarian, lung and pancreatic cancer) women (Table 2). In the Cox models, in which only the baseline ET measurement was used, the sample size was, at most, 1936 lower than that in the joint model due to missing baseline measurements. The frequency of cancer was also slightly reduced (Table 2).

In the joint models, there was statistical evidence at the 5% level of a positive association between ET and the risk of three of the six cancer types (Table 2). The strongest association was with breast cancer (HR, 1.21; 95% CI, 1.09–1.36; $P=0.001$). This model was the only instance in which a Weibull baseline hazard was not suitable ($P=0.0002$). The 1-year absolute risk of breast cancer for a woman aged 50 with an ET of 5 mm was 165 in 100,000 vs 136 in 100,000 for an ET of 2.5 mm. For ovarian cancer, the HR was 1.39 (95% CI, 1.06–1.82; $P=0.018$) and for lung cancer the HR was 1.25 (95% CI, 1.02–1.54; $P=0.036$). A sensitivity analysis specifically for lung cancer, that additionally included alcohol intake and smoking as covariates, yielded a higher HR (1.35; 95% CI, 0.98–1.86), although it was not statistically significant ($P=0.066$) due to fewer events (157/25,469).

The association between ET and cancer risk was not significant for colorectal (HR, 1.15; $P=0.150$), pancreatic (HR, 0.99; $P=0.947$) or bladder (HR, 0.86; $P=0.542$) cancer. One-, 5- and 10-year absolute risks for breast, ovarian and lung cancer at selected ages and ETs are shown in Table 3. For example, the 10-year risk in women at age 60 with an ET of 10 mm is 4.5% for breast cancer, 1.2% for ovarian cancer and 0.9% for lung cancer.

Table 2 also shows the results of the Cox models for all nine cancers, using only the baseline ET measurement. A significant association at the 5% level was noted only for ovarian cancer (HR, 1.22; 95% CI, 1.04–1.42; $P=0.015$). HR was <1 for each of the three cancers not fitted by a joint model (gastric: HR, 0.79; liver: HR, 0.86 and NHL: HR, 0.81), but with $P$-values >0.1.

Figure 3 shows the estimated hazard functions for the six cancers from the joint models, calculated for ET values of 2.5 mm and 5 mm. Note that overlap of the 95% CI should not be used as an indicator of the significance of the HR values, as the respective hazard functions are not independent. The hazard functions for most of the cancers show increasing risk with age, although the Weibull distribution forces the functions to be monotonic. The exception is breast cancer, for which, after about age 65, there is a gradual decline in the risk associated with ET.

**DISCUSSION**

In this prospective cohort study of 38,105 postmenopausal women with a combined total of 267,567 ET measurements and over 400,000 years of follow-up, we report on the association between ET measured using TVS, as a functional surrogate for cumulative circulating estrogen, and the risk of nine non-endometrial cancers that may be affected by estrogen exposure. A doubling of ET was associated with an increased risk of breast (21%), ovarian (39%) and lung (25%) cancer. There was no association with pancreatic cancer, a non-significant increased risk of colorectal cancer and a non-significant decreased risk of bladder, liver and gastric cancers and NHL.

Key strengths of this study include its prospective multicenter design, the large cohort size, measurement of ET using a standard protocol and similar ultrasound machines across the centers and over time, completeness of cancer notification through linkage to national cancer registries and long-term follow-up of the cohort. We report for the first time on the association between ET and eight (ovarian, lung, colorectal, pancreatic, bladder, gastric, liver and NHL) cancers. The only prior study investigating the association between ET and breast cancer either used only the baseline ET measurement or incorporated serial...
Table 1 Baseline and follow-up characteristics of cohort of 36 168 women undergoing annual transvaginal ultrasound examinations, who had endometrial thickness measurement at baseline, overall and according to baseline endometrial thickness

| Characteristic                        | Overall (n = 36 168) | < 3 mm (n = 18 429) | 3 mm to < 5 mm (n = 11 694) | ≥ 5 mm (n = 6045) | P       |
|--------------------------------------|----------------------|---------------------|----------------------------|------------------|---------|
| **Baseline**                         |                      |                     |                            |                  | < 0.0001|
| Age (years)                          |                      |                     |                            |                  |         |
| ≥ 50 to < 60                         | 16 840               | 8197 (48.7)         | 5742 (34.1)                | 2901 (17.2)      |         |
| ≥ 60 to < 70                         | 15 321               | 8110 (52.9)         | 4731 (30.9)                | 2480 (16.2)      |         |
| ≥ 70                                 | 4007                 | 2122 (53.0)         | 1221 (30.5)                | 664 (16.6)       |         |
| Age at menopause (years)             |                      |                     |                            |                  | < 0.0001|
| < 45                                 | 3908                 | 2184 (55.9)         | 1181 (30.2)                | 543 (13.9)       |         |
| 45 to < 55                           | 27 892               | 14 304 (51.3)       | 9020 (32.3)                | 4568 (16.4)      |         |
| ≥ 55                                 | 4368                 | 1941 (44.4)         | 1493 (34.2)                | 934 (21.4)       |         |
| BMI (kg/m²)                          |                      |                     |                            |                  | < 0.0001|
| < 25                                 | 15 994               | 8799 (55.0)         | 4930 (30.8)                | 2265 (14.2)      |         |
| ≥ 25 to < 30                         | 13 147               | 6721 (51.1)         | 4238 (32.2)                | 2188 (16.6)      |         |
| ≥ 30                                 | 7027                 | 2909 (41.4)         | 2526 (36.0)                | 1592 (22.7)      |         |
| Parity                               |                      |                     |                            |                  | < 0.0001|
| Nulliparous                          | 4313                 | 2469 (57.2)         | 1186 (27.5)                | 658 (15.3)       |         |
| Parous                               | 31 855               | 15 960 (50.1)       | 10 508 (33.0)              | 5387 (16.9)      |         |
| OCP use                              |                      |                     |                            |                  | 0.021   |
| Never                                | 14 207               | 7368 (51.9)         | 4505 (31.7)                | 2334 (16.4)      |         |
| Ever                                 | 21 961               | 11 061 (50.4)       | 7189 (32.7)                | 3711 (16.9)      |         |
| Current HRT use                      |                      |                     |                            |                  | < 0.0001|
| No                                   | 30 030               | 16 383 (54.6)       | 9379 (31.2)                | 4268 (14.2)      |         |
| Yes                                  | 6138                 | 2046 (33.3)         | 2315 (37.7)                | 1777 (29.0)      |         |
| First scan*                          |                      |                     |                            |                  | < 0.0001|
| Current HRT use                      |                      |                     |                            |                  |         |
| No                                   | 31 966               | 17 126 (53.6)       | 10 128 (31.7)              | 4712 (14.7)      |         |
| Yes                                  | 4202                 | 1303 (31.0)         | 1566 (37.3)                | 1333 (31.7)      |         |
| Follow-up questionnaire†             |                      |                     |                            |                  | 0.254   |
| Smoker                               |                      |                     |                            |                  |         |
| Never                                | 16 018               | 8306 (51.9)         | 5066 (31.6)                | 2646 (16.5)      |         |
| Ever                                 | 8395                 | 4266 (50.8)         | 2735 (32.6)                | 1394 (16.6)      |         |
| Alcohol (units/week)                 |                      |                     |                            |                  | < 0.0001|
| None                                 | 6384                 | 3275 (51.3)         | 1948 (30.5)                | 1161 (18.2)      |         |
| ≤ 3                                  | 10 566               | 5430 (51.4)         | 3430 (32.5)                | 1706 (16.1)      |         |
| 4–10                                 | 7701                 | 4053 (52.6)         | 2490 (32.3)                | 1158 (15.0)      |         |
| ≥ 11                                 | 3423                 | 1762 (51.5)         | 1089 (31.8)                | 572 (16.7)       |         |

Data are given as n or n (%) . * Will differ at other scans. † Approximately 77% completed, 3.5 years post-randomization. BMI, body mass index; HRT, hormone-replacement therapy; OCP, oral contraceptive pill.

Figure 2 Reference centile curves of endometrial thickness (ET) measured using transvaginal ultrasound in postmenopausal women aged 50–80 years, who were not diagnosed with one of nine investigated non-endometrial cancers or endometrial cancer. Curves are derived from standalone mixed model, which smooths out impact of measurement error at population level.
Table 2 Associations between serial and baseline measurements of endometrial thickness (ET) on transvaginal ultrasound and different non-endometrial cancers

| Cancer     | Total women (n) | Cancer (n) | HR (95% CI) | P     | Total women (n) | Cancer (n) | HR (95% CI) | P     |
|------------|----------------|------------|-------------|-------|----------------|------------|-------------|-------|
| Breast     | 38 078         | 1398       | 1.213 (1.085–1.357) | 0.001 | 36 152         | 1338       | 1.063 (0.997–1.133) | 0.064 |
| Ovarian    | 38 105         | 222        | 1.390 (1.059–1.824) | 0.018 | 36 169         | 211        | 1.215 (1.039–1.420) | 0.015 |
| Colorectal | 38 099         | 495        | 1.147 (0.952–1.381) | 0.150 | 36 164         | 464        | 1.037 (0.932–1.155) | 0.503 |
| Lung       | 38 105         | 381        | 1.251 (1.015–1.543) | 0.036 | 36 169         | 364        | 1.029 (0.911–1.163) | 0.645 |
| Pancreatic | 38 105         | 94         | 0.985 (0.640–1.518) | 0.947 | 36 169         | 85         | 0.959 (0.746–1.232) | 0.742 |
| Bladder    | 38 104         | 79         | 0.858 (0.524–1.404) | 0.542 | 36 169         | 76         | 0.877 (0.668–1.151) | 0.345 |
| Gastric    | 38 104         | 62         | —‡          |       | 36 169         | 59         | 0.789 (0.579–1.076) | 0.135 |
| Liver      | 38 105         | 38         | —‡          |       | 36 168         | 33         | 0.858 (0.567–1.299) | 0.468 |
| NHL        | 38 104         | 52         | —‡          |       | 36 168         | 50         | 0.810 (0.579–1.133) | 0.218 |

Hazard ratios (HR) represent doubling of ET. All models adjusted by current hormone-replacement therapy use, body mass index, age at last period, parity and oral contraceptive pill use. *Joint models included longitudinal and time-to-event data. †Cox models included baseline measurements only. ‡Joint models did not converge for gastric and liver cancer and non-Hodgkin’s lymphoma (NHL).

Table 3 One-, 5- and 10-year absolute risks (AR) for breast, ovarian and lung cancer, according to endometrial thickness (ET) and age

| Age | 2.5 mm | 5 mm | 10 mm | 2.5 mm | 5 mm | 10 mm | 2.5 mm | 5 mm | 10 mm |
|-----|--------|------|-------|--------|------|-------|--------|------|-------|
| Breast cancer |        |      |       |        |      |       |        |      |       |
| 50 years   | 136    | 165  | 201   | 832    | 1008 | 1222  | 2051   | 2483 | 3005  |
| 55 years   | 215    | 261  | 317   | 1229   | 1490 | 1805  | 2750   | 3327 | 4022  |
| 60 years   | 291    | 353  | 428   | 1540   | 1865 | 2258  | 3112   | 3763 | 4548  |
| 65 years   | 327    | 396  | 480   | 1597   | 1934 | 2342  | 3055   | 3694 | 4465  |
| 70 years   | 309    | 375  | 454   | 1481   | 1795 | 2173  | 2827   | 3420 | 4134  |
| Ovarian cancer |      |      |       |        |      |       |        |      |       |
| 50 years   | 47     | 65   | 90    | 243    | 337  | 468   | 510    | 708  | 982   |
| 55 years   | 52     | 72   | 100   | 268    | 372  | 517   | 560    | 778  | 1079  |
| 60 years   | 57     | 79   | 109   | 293    | 407  | 566   | 611    | 848  | 1177  |
| 65 years   | 62     | 86   | 119   | 319    | 443  | 615   | 662    | 919  | 1275  |
| 70 years   | 67     | 95   | 126   | 344    | 478  | 664   | 713    | 990  | 1373  |
| Lung cancer |        |      |       |        |      |       |        |      |       |
| 50 years   | 15     | 19   | 24    | 94     | 118  | 147   | 242    | 303  | 379   |
| 55 years   | 25     | 31   | 39    | 148    | 185  | 232   | 373    | 466  | 583   |
| 60 years   | 38     | 48   | 60    | 225    | 281  | 352   | 554    | 693  | 866   |
| 65 years   | 57     | 71   | 89    | 330    | 413  | 516   | 800    | 1000 | 1249  |
| 70 years   | 82     | 102  | 128   | 471    | 589  | 737   | 1126   | 1407 | 1757  |

Data are given as risk per 100,000 women.

less day-to-day biological variability than does the level of circulating estrogen. Furthermore, ET likely reflects the cumulative estrogen exposure, and hence, is a better measure of cancer risk than is estradiol (E2) level.

A doubling of ET resulted in a HR of 1.21 for breast cancer, compared with the HR of 2.00 reported by Felix et al.24, when comparing the risk in women with ET ≥5 mm vs <3 mm. However, the latter report was based on 91 breast cancers compared with 1398 in this analysis, which therefore provides more precise estimates and much stronger statistical association. Breast cancer was the only analysis for which the estimated hazard function did not rise monotonically with age, and use of a cubic spline demonstrated a notable decline in the risk associated with increasing ET in women over 65 years of age. This may reflect the age range (50–70 years) of the NHS breast-screening program and associated overdiagnosis in women of these ages. In postmenopausal women, an increase in breast cancer risk has been reported previously in women with high levels of endogenous sex hormones, including E2 and estrone, with odds ratios of 2.00 and 2.19, respectively, when the highest quintiles are compared to the lowest3.

We found a strong association between a doubling of ET and ovarian cancer (HR, 1.39; P = 0.018). Trabert et al.31 reported a modest association of higher levels of estrone and other estrogen metabolites with ovarian cancer, which was limited to non-serous histotypes. The link between ovarian cancer and exogenous hormones is now well established, with data from the Women’s Health Initiative (WHI) suggesting that estrogen-plus-progestin therapy may increase ovarian cancer risk, most notably for serous histotypes (relative risk, 1.53)6.
Figure 3 Estimated hazard functions for breast (a; hazard ratio (HR), 1.213; 95% CI, 1.085–1.357), ovarian (b; HR, 1.390; 95% CI, 1.059–1.824), lung (c; HR, 1.251; 95% CI, 1.015–1.543), colorectal (d; HR, 1.147; 95% CI, 0.952–1.381), pancreatic (e; HR, 0.985; 95% CI, 0.640–1.518) and bladder (f; HR, 0.858; 95% CI, 0.524–1.404) cancer, using joint models in women aged 50–80 years, calculated for endometrial thickness (ET) of 5 mm (long dashed line, with shaded 95% CI) and 2.5 mm (short dashed line, with shaded 95% CI), meaning ratio (doubling of ET) equates to model HR. Both functions are estimated for no current hormone-replacement therapy use, parity of one, no oral contraceptive pill use, body mass index of 25 kg/m² and age at last menstrual period of 50 years and presented per 100 000 women.

additional covariates of alcohol and smoking, which were available for only a subset of women. This is in keeping with the latest belief that estrogen is responsible for augmenting the risk of lung cancer in smokers. One suggestion is that circulating estrogen plays a role in modifying ER-beta levels, which are known to inhibit tumor growth.

Colorectal cancer was the only other common cancer in our study (n = 495), and despite an increase in risk (HR, 1.15), the association with a doubling of ET was not significant at the 5% level (P = 0.15). Although increasing circulating estrone has been reported to be associated with an elevated risk of colorectal cancer, the majority of publications suggest that estrogen and its ER-beta receptor are protective for this cancer. Data from the WHI study and population-based registries in Norway have demonstrated a decrease in colorectal cancer risk with short term/current use of estrogen-plus-progestin HRT.

Investigation of the five other assessed cancers was limited by their low incidence, although the association was estimated to be essentially null only for pancreatic
One of the benefits of using ET as a proxy/surrogate marker for circulating estrogen is its relative ease of measurement. Serum E2 levels are usually measured using a radioimmunoassay. Mass spectrometry is used increasingly because it provides greater specificity and sensitivity, especially for the low E2 concentrations observed in postmenopausal women. However, in addition to cost and run time, there are limited data available on the discrepancies between individual spectrometry-based assays. Findings from one study indicated that interfering compounds might cause E2 levels to be 10-times higher than the true value.

In conclusion, in this study exploring the association between ET measured using TVS and the risk of nine non-endometrial, potentially hormone-sensitive, cancers in postmenopausal women, we found that high and/or increasing ET was associated significantly with an increased risk of breast, ovarian and lung cancer. This suggests that ET may merit inclusion in future risk prediction models for these cancers. While our findings need further validation, clinicians might wish to assess appropriately women with high or increasing ET measurements on TVs who do not have endometrial cancer.

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Disclosure

U.M. has stocks in Abcodia Ltd., awarded to her by University College London. I.J. is a coinventor of the Risk of Ovarian Cancer Algorithm (ROCA), which has been licensed to Abcodia Ltd. by Massachusetts General Hospital (MGH) and Queen Mary University of London (QMUL). I.J. has a financial interest in Abcodia Ltd., as a shareholder and director, and is entitled to royalty payments via MGH and QMUL from any commercial use of the ROCA.

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**SUPPORTING INFORMATION ON THE INTERNET**

The following supporting information may be found in the online version of this article:

- Appendix S1 Supplementary methods