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Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass ☆

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HIGHLIGHTS

- HE4 performs equivalent to CA125 in stratifying women with a pelvic mass.
- ROMA is valuable as a first line marker for referring high risk patients to tertiary centers.
- ROMA is as good as the ultrasound dependent RMI in differentiating pelvic masses.

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ABSTRACT

Objective. Diagnostic factors are needed to improve the currently used serum CA125 and risk of malignancy index (RMI) in differentiating ovarian cancer (OC) from other pelvic masses, thereby achieving precise and fast referral to a tertiary center and correct selection for further diagnostics. The aim was to evaluate serum Human Epididymis protein 4 (HE4) and the risk of ovarian malignancy algorithm (ROMA) for these purposes.

Methods. Serum from 1218 patients in the prospective ongoing pelvic mass study was collected prior to diagnosis. The HE4 and CA125 data were registered and evaluated separately and combined in ROMA and compared to RMI.

Results. 809 benign tumors, 79 borderline ovarian tumors, 252 OC (64 early and 188 late stage), 9 non-epithelial ovarian tumors and 69 non-ovarian cancers were evaluated. Differentiating between OC and benign disease the specificity was 62.2 (CA125), 63.2 (HE4), 76.5 (ROMA) and 81.5 (RMI) at a set sensitivity of 94.4 which corresponds to RMI = 200. The areas under the curve (AUC) were 0.854 (CA125), 0.864 (HE4), 0,897 (ROMA) and 0.905 (RMI) for benign vs. early stage OC. For premenopausal benign vs. OC AUC were 0.925 (CA125), 0.905 (HE4), 0.909 (ROMA) and 0.945 (RMI).

Conclusion. HE4 and ROMA helps differentiating OC from other pelvic masses, even in early stage OC. ROMA performs equally well as the ultrasound depending RMI and might be valuable as a first line biomarker for selecting high risk patients for referral to a tertiary center and further diagnostics. Further improvements of HE4 and ROMA in differentiating pelvic masses are still needed, especially regarding premenopausal women.

Introduction

Each year, ovarian cancer (OC) causes approximately 390 deaths in Denmark [1]. This makes OC the fourth most frequent cancer causing death for women [2]. Approximately 470 new cases of OC are found per year among Danish women [3]. OC is most common among postmenopausal women (80%), but can occur in any age [4].

According to the Danish Gynecologic Cancer Database (DGCD) the 5-year overall survival rate for OC is 38.6%. The 5-year survival for the

☆ From the Danish "pelvic mass" ovarian cancer study.

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four International Federation of Gynecology and Obstetrics (FIGO) stages are 83.2% for stage I, 52.9% for stage II, 22.8% for stage III and 10.7% for stage IV OC.

Unfortunately, approximately 65% of OC patients are diagnosed at a late stage (FIGO stage III–IV) [3]. The relatively high frequency, late diagnosis and therefore poor prognosis are considerable clinical issues and additional diagnostic and prognostic factors are needed.

In case of a suspicious pelvic mass or symptoms a serum CA125 test is requested and the patient is referred to an abdominal and vaginal ultrasound. Based on menopausal status, ultrasound findings (US) and serum CA125 level the risk malignancy index (RMI) is calculated. If RMI is ≥200 the patient enters the national cancer fast track guidelines, which includes referral to a tertiary gynecological oncological center where the patient is examined by a gynecologic oncologist, offered PET/CT and hereafter discussed at a multidisciplinary team meeting, where an individual treatment is planned. In case PET/CT indicate OC and the possibility for radical surgery, primary surgery (laparoscopy or laparotomy) was offered — if PET/CT indicated advanced OC with no possibility for radical surgery, biopsies were sampled neoadjuvant chemotherapy was offered. The diagnostic evaluation and operation must be completed in less than 16 working days or start on neoadjuvant chemotherapy in less than 18 working days.

Several studies have demonstrated that operative treatment by gynecologic oncologists versus general gynecologists is an important prognostic factor because of a higher debulking rate and fewer postoperative complications [5–8]. Preoperative optimal differentiation between benign and malignant pelvic masses is therefore of great clinical importance for optimal referral and patient care, and a clinical algorithm with a high sensitivity and specificity to triage these patients is needed.

RMI is presently the most accurate tool for stratifying patients into high and low risk groups. Two prospective multicenter studies including 1159 and 548 patients respectively showed for RMI a sensitivity of 92% and 81% and a specificity of 82% and 85% respectively at a cut-off value of 200 [9,10]. CA125 has so far been the best-performing single tumor marker used in diagnostics and monitoring of OC. CA125 is found elevated in several benign gynecologic and non-gynecologic diseases leading to unnecessary surgery for a large group of patients with a benign pelvic mass. Furthermore, approximately 20% of OC patients have normal or only marginally elevated serum CA125, a phenomenon especially seen in early stage OC [11,12].

Several biomarkers have been examined to find alternative or additive markers that can distinguish between a benign pelvic mass and OC. Currently Human Epididymis protein 4 (HE4) seems to be a promising biomarker of OC [13,14].

HE4 is a glycoprotein, over expressed by epithelial OC. High concentrations have been detected in serum from OC patients, especially patients with serous and endometrioid adenocarcinoma [15–17]. Expression of HE4 in normal tissue is low, higher in non-ovarian cancer tissue and with the highest expression found in OC tissue [18]. HE4 as a single tumor marker has been reported as good as CA125 for detection of OC. Combined, HE4 and CA125 enhance the sensitivity and specificity for differentiating OC [13,14]. Moore et al. developed the risk of ovarian malignancy algorithm (ROMA), a simple biomarker based algorithm compared to RMI which require US [19]. Evaluation of ROMA has been diverging in relatively small studies [17,19–21].

The aim of this study was to investigate HE4 as a differential diagnostic marker for OC, separately and combined with CA125 in ROMA. A comparison of HE4 and ROMA with CA125 and RMI also seems relevant.

Materials and methods

Patients

From September 2004 to January 2010 a total of 1218 women were included in the “pelvic mass” study; a prospective ongoing study with the objectives to identify diagnostic and prognostic factors for OC in women with a pelvic mass. The participants were included when admitted to the Gynecologic Clinic, Rigshospitalet, Denmark for surgery due to a pelvic mass or pelvic pains potentially caused by a malignant disease or endometriosis. All patients were informed verbally and in writing and invited to participate in the study after written consent. Patients with preoperative known relapse of a previous cancer or an active cancer other than OC were excluded.

Patients were examined according to our cancer fast track guidelines. If radical surgery was found possible the patient was operated by a gynecologic oncologist, and radical resection was intended. If radical surgery was not possible, the patients were offered biopsy for diagnosis and staging followed by neoadjuvant chemotherapy. All tissue specimens were examined by a pathologist specialized in gynecologic pathology.

All patients were registered online in the DGCD. Clinical data, treatment information and survival status are updated continuously.

The Danish Ethical Committee approved the protocol according to the rules used in the International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) recommendations and the Helsinki and Tokyo conventions (KF01-227/03 and KF01-143/04, H-3-2010-022).

Methods

Blood samples were collected in conjunction with routine blood testing of the patients within 2 weeks prior to surgery and were centrifuged and fractionated into serum within 6 h after collection. Serum was stored in aliquots at −80 °C until analyzed.

Serum CA125 and HE4 were quantitatively determined on the ARCHITECT I 2000sr System from Abbott Diagnostics, a two-step chemiluminescent microparticle immunoassay (CMIA).

To calculate ROMA, serum-HE4, serum-CA125 and menopausal status were used. Patients were considered postmenopausal 1 year after cessation of menstrual bleeding. Hysterectomized patients were considered postmenopausal at the age of 50 or older. A predictive index (PI) was calculated using the following equations:

$$\text{Premenopausal}: \text{PI} = -12 + 2.38 \times \text{LN}(\text{HE4}) + 0.0626 \times \text{LN}(\text{CA125})$$

$$\text{Postmenopausal}: \text{PI} = -8.09 + 1.04 \times \text{LN}(\text{HE4}) + 0.732 \times \text{LN}(\text{CA125}).$$

The ROMA-value (predictive value) was then calculated using the following equation:

$$\text{ROMA}(\%) = e^{\text{PI}} / \left(1 + e^{\text{PI}}\right) \times 100.$$

To calculate RMI US (coded 1 or 3), menopausal status (coded 1 or 3) and serum CA125 were used in the following equation:

$$\text{RMI} = \text{US} \times \text{menopausal status} \times \text{CA125}.$$

The RMI cut-off value is 200 in Denmark. The sensitivity (SN) and specificity (SP) at this cut-off value was used to compare HE4 and ROMA to RMI.

Statistical analysis

Clinical data from DGCD were used for statistical analyses. HE4 and CA125 data were registered and evaluated statistically separately and combined in ROMA. The ability of CA125, HE4 and ROMA to differentiate OC from other pelvic masses was evaluated by setting the SN at the same level as SN for RMI at a cut-off value at 200 for comparison of the respective SP. The accuracy of HE4, CA125, RMI and ROMA to discriminate between different subgroups in our patient material was evaluated by using the receiver operating characteristic (ROC) curve analysis.

The statistical significance was demonstrated by 95% CI. Statistical analyses were performed by using IBM SPSS Statistics 19.0.

Results

Of the 1218 patients 66% (n = 809) had benign ovarian disease, 6% (n = 79) had a borderline ovarian tumor, 21% (n = 252) had epithelial OC, 1% (n = 9) had non-epithelial ovarian tumors and 6% (n = 69) had non-ovarian cancers. Of the 252 patients with epithelial OC 15.9% (n = 40) had FIGO stage I cancer, 9.5% (n = 24) FIGO stage II cancer, 56.7% (n = 143) FIGO stage III cancer and 17.9% (n = 45) FIGO stage IV cancer.

Median age was 51 years (range 16–90). 597 women were premenopausal and 621 postmenopausal (Table 1).

The median HE4 level was 53.4 pmol/L (range 19–1426) for benign tumors, 81.8 pmol/L (range 29–1109) for borderline tumors and 436 pmol/L (range 16–15000) for OC.

The median CA125 level was 28.7 U/ml (range 3–3586) for benign tumors, 87.6 U/ml (range 10–6410) for borderline tumors and 647 U/ml (range 10–10000) for OC.

The median ROMA value was 10.8 (range 0.9–99.6) for benign disease, 32.0 (range 2.2–96.9) for borderline ovarian tumors and 95.7 (range 0.6–1000.0) for OC.

Finally, the median RMI value was 48 (range 2–17,154) for benign disease, 360 (range 13–15,264) for borderline ovarian tumors and 3330 (range 6–153,432) for OC (Table 1).

Evaluation of the ability to differentiate epithelial OC from benign pelvic masses showed that SN of RMI was 94.4 and SP was 81.5 using a cut-off value of 200. At SN of 94.4, SP was 62.2 for CA125, 63.2 for HE4 and 76.5 for ROMA. No significant superiority of HE4 compared to CA125 was found. When dividing patients in early and late stage OC, SP for RMI was superior in both early stage (SP 65.3) and late stage OC (SP 91.1). Similarly for premenopausal women RMI was superior with SP at 70.0, but for postmenopausal women ROMA was superior (SP 73.5) in differentiating between benign and malignant disease (Table 2).

The ability to differentiate benign disease and OC was evaluated at a set SP at 75% to compare with previous studies. SN was 91.7 for CA125, 91.3 for HE4, 94.8 for ROMA and 96.0 for RMI. RMI showed a non-significant tendency to be superior to ROMA in both early (SN 89.1) and late stage OC (SN 98.4). For postmenopausal women CA125 and ROMA was superior, both with a SN at 92.6 (Table 2).

AUC was 0.930 for CA125, 0.939 for HE4, 0.954 for ROMA and 0.958 for RMI when distinguishing between benign disease and OC. For respectively early and late stage OC AUC was 0.854 and 0.953 for CA125, 0.864 and 0.964 for HE4, 0.897 and 0.972 for ROMA and 0.905 and 0.976 for RMI.

AUC for premenopausal women was 0.925 for CA125, 0.905 for HE4, 0.909 for ROMA and 0.945 for RMI. For postmenopausal women AUC was 0.921 for CA125, 0.922 for HE4, 0.946 for ROMA and 0.930 for RMI.

Subgroup analysis of the ability to differentiate endometriosis from OC gave an AUC of 0.908 for CA125, 0.960 for HE4, 0.970 for ROMA and 0.976 for RMI.

Analysis of differentiation between borderline ovarian tumors and OC showed an AUC of 0.824 for CA125, 0.865 for HE4, 0.868 for ROMA and 0.833 for RMI. For differentiation of borderline ovarian tumors and benign ovarian disease the AUC was 0.716 for CA125, 0.730 for HE4, 0.770 for ROMA and 0.827 for RMI.

Analysis of OC versus non-ovarian malignancies showed an AUC of 0.725 for CA125, 0.782 for HE4, 0.769 for ROMA and 0.714 for RMI. None of the above described AUC differences of ROMA and RMI were significant.

Finally the ability to differentiate OC from all other patient groups was analyzed, resulting in AUC of 0.906 for CA125, 0.922 for HE4, 0.933 for ROMA and 0.929 for RMI (Table 2 and Fig. 1).

Suggested cut-off values for HE4 and ROMA were examined. At a cut-off value at 150 pmol/L for HE4 (Fujirebio [25]) SN was 78.6 and SP 96.0. At a cut-off value at 140 pmol/L (Abbott Diagnostics [26]) SN was 79.4 and SP 94.9. For premenopausal women Abbott recommends a cut-off value at 70 pmol/L for HE4 and 7.4 for ROMA giving a SN at 79.6 and 93.9 respectively and a SP at 82.5 and 52.6 respectively. For postmenopausal women Abbott recommends a cut-off value at 140 pmol/L for HE4 and 25.3 for ROMA giving a SN at 81.8 and 97.5 respectively and a SP at 89.6 and 57.0 respectively (Table 3).

Discussion

Accurate referral of patients with a pelvic mass is crucial. Benign pelvic masses can be treated locally, whereas pre-operative evaluation and treatment of patients suspected of OC should take place at a tertiary center by gynecologic oncologists to enhance the prognosis of OC [5–8]. As a consequence of centralization of treatment of OC in Denmark [3], detection of new biomarkers and algorithms that can help differentiate OC from other pelvic masses are of major importance.

Several studies have evaluated the clinical usefulness of HE4 and ROMA. In 2003 Hellstrom et al. described HE4 as a promising serum marker for OC in postmenopausal women (n = 121) with OC, benign disease and a control group. Based on their results it was concluded that larger studies were needed [13].

Moore et al. found a significant increased in SN and SP when combining HE4 and CA125 [14]. The ROMA algorithm was developed and tested in a study evaluating 531 pelvic mass patients. Analyzing benign masses versus OC, SN was 93.8% at a set SP at 75%. When subdividing according to menopausal status, SN was 88.9% for premenopausal and 94.5% for postmenopausal, indicating that ROMA could be a valuable tool in referral of women with a pelvic mass to appropriate surgical centers [19]. The results by Moore et al. is in agreement with our results when using a set SP at 75% that showed a SN at 94.8% for all benign and OC patients, SN at 91.8 for premenopausal and SN at 92.6 for postmenopausal women. In a later study by Moore et al. (n = 457) ROMA was compared to RMI. ROMA had a significantly higher SN at 94.3% (AUC 0.953) compared to RMI with a SN at 84.6% (AUC 0.870) at a set SP of 75% [21]. The results by Moore et al. could not be confirmed in our study. We found RMI performed slightly better (SN 96.0) than ROMA (SN 94.8) at a set SP at 75%, and AUC analysis proved that RMI and ROMA performed equally in differentiating benign pelvic masses and OC. As our study cohort is based on referred patients it may be expected that an algorithm perform better when used by the general physician. ROMA could potentially optimize and shorten the time spend before high risk patients are admitted to a tertiary center,

Table 1
Baseline data.

	Benign	Borderline ovarian tumor	Epithelial OC [early/late]	Non-epithelial tumors	Non-ovarian cancers
Numbers (pre-/post-menopausal)	809 (530/279)	79 (24/55)	252 [64/188] (49/203)	9 (4/5)	69 (14/55)
Age (median, range)	42 (19–90)	60 (22–88)	64 (16–89)	47 (31–72)	64 (25–87)
HE4 (pmol/l) (median, range)	53.4 (19–1426)	81.8 (29–1109)	436 (16–15,000)	68 (22–250)	110 (28–7389)
CA125 (U/ml) (median, range)	28.7 (3–3586)	87.6 (10–6410)	647 (10–10,000)	26 (11–623)	159 (8–4586)
ROMA (median, range)	10.7 (0.9–99.6)	32.0 (2.2–96.9)	95.7 (0.6–1000.0)	17.0 (1.2–12.0)	61.2 (2.0–99.9)
RMI (median, range)	48 (2–17,154)	360 (13–15,264)	3330 (6–153,432)	135 (12–6156)	747 (13–77,400)

Table 2
Benign and OC patients.

		CA125	HE4	ROMA	RMI
SP (%) at SN 94.4%	All	62.2	63.2	76.5	81.5
	Early/late stage OC	51.9/83.3	52.9/82.8	61.8/88.8	65.3/91.1
	Pre-/postmenopausal	51.2/69.2	37.7/53.0	40.2/73.5	70.0/68.8
SN (%) at SP 75.0%	All	91.7	91.3	94.8	96.0
	Early/late stage OC	78.1/96.3	78.1/95.7	87.5/97.3	89.1/98.4
	Pre-/postmenopausal	89.8/92.6	89.8/89.2	91.8/92.6	93.9/91.6
ROC-AUC (95% CI)	All	0.930 (0.911–0.948)	0.939 (0.920–0.958)	0.954 (0.938–0.970)	0.958 (0.944–0.971)
	Early stage OC	0.854 (0.811–0.897)	0.864 (0.815–0.912)	0.897 (0.853–0.940)	0.905 (0.866–0.944)
	Late stage OC	0.955 (0.937–0.973)	0.965 (0.947–0.982)	0.973 (0.959–0.987)	0.976 (0.966–0.985)
	Premenopausal	0.925 (0.876–0.975)	0.905 (0.844–0.966)	0.909 (0.849–0.969)	0.945 (0.901–0.989)
	Postmenopausal	0.921 (0.897–0.945)	0.922 (0.896–0.947)	0.946 (0.927–0.964)	0.930 (0.908–0.951)

since US at a gynecologist is not necessary for ROMA, opposite RMI. Oncologic US assessment may then be performed at the tertiary center as it requires a high training level. A pure biomarker algorithm is more objective, which may be an argument for the better suitability of ROMA in a primary care setting.

An independent validation study by Van Gorp et al. evaluating 389 pelvic mass patients illustrated that HE4 and ROMA did not supply significantly in the differentiation of OC from other pelvic masses compared to CA125 alone [17]. Opposite, Montagnana et al. illustrated a contribution when using HE4 or ROMA compared to CA125 alone, but no improvement when using ROMA compared to HE4 alone. The ROMA SN was in Montagnana's study (n = 104) compared to the results from Moore et al., and they found a markedly lower SN (74.5%) compared to Moore et al. (94.3%), unfortunately a comparison is not possible because of the different SP (81.6% in Montagnana's study vs. 75% in Moore's study) [19,20]. The two described validation studies by Van Gorp and Montagnana did not include comparison of HE4 and ROMA to RMI, which is used as standard in Denmark.

Both serum CA125 and RMI are inaccurate tools of differentiation in early stage OC. Moore et al. described that HE4 had significantly higher SN at a set SP than CA125 when analyzing stage I OC (n = 13) [14]. In our study we were not able to confirm this tendency, which may be explained by the difference in study cohorts.

In a later study by Moore et al. ROMA was by far the greatest differential tool (AUC 0.909) compared to RMI (AUC 0.762) to detect early stage OC [21]. We could not confirm this tendency, but found that ROMA (AUC 0.897) was equivalent to RMI (AUC 0.905), indicating that the tumor marker based algorithm ROMA could be as valuable as RMI to detect early disease.

Other studies have described HE4 as a potential better marker compared to CA125 in the diagnostic process of premenopausal women with a pelvic mass [14,20,22], which we were not able to confirm as CA125 and RMI were superior to HE4 and ROMA. This indicates a need to optimize HE4 and ROMA for premenopausal women. Our patient characteristic differs from the other studies because of a relatively large percentage of patients with endometriosis (36.7%). When stratifying endometriosis from other benign diseases, HE4 was found superior to CA125, a tendency previously described in other studies [21,23,24]. We found RMI and ROMA comparable, indicating that the large proportion of patients with endometriosis could not explain the diverse results for premenopausal women. ROMA improved differentiation of OC and benign masses in postmenopausal women.

HE4 and ROMA improved differentiation of borderline ovarian tumors and OC, but no improvement was seen in differentiation of borderline ovarian tumors and benign disease.

A significant enhancement using HE4 (AUC 0.782) and ROMA (AUC 0.769) compared to CA125 (AUC 0.725) and RMI (AUC 0.714) in differentiating OC from non-ovarian cancers was observed. ROMA could therefore be a valuable tool for correct admission of patients with non-ovarian cancers.

Van Gorp et al demonstrated that standardized US performed/supervised by experienced sonographers at a tertiary center was

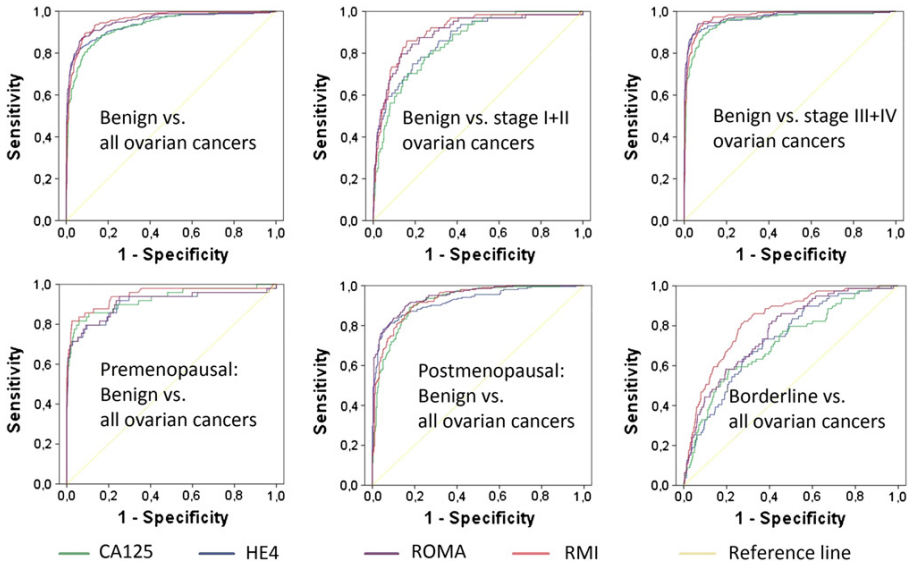

Fig. 1. ROC curves.

Table 3
Suggested cut-off values for HE4 and ROMA.

HE4 and ROMA:	Suggested cut-offs	SN	SP
HE4 (pmol/L)[a]	**150**	78.6	96.0
HE4 (pmol/L)[b]	**140**	79.4	94.9
HE4 (pmol/L) premenopausal[b]	**70**	79.6	82.5
HE4 (pmol/L) postmenopausal[b]	**140**	81.8	89.6
ROMA premenopausal[b]	**7.4**	93.9	52.6
ROMA postmenopausal[b]	**25.3**	97.5	57.0

[a] Fujirebio Diagnostics [25].
[b] Abbott Diagnostics [26].

superior (both subjective assessment and included in RMI) to the tumor marker based ROMA [27]. This indicates the need to include US in an algorithm, if HE4 should be a valuable diagnostic tool after referral to tertiary centers.

This prospective ongoing study is one of the largest cohorts investigated so far, including a total of 1218 pelvic mass patients. In conclusion, ROMA and RMI are equally in differentiating between benign and malignant pelvic masses. We found that ROMA might be valuable as a first line marker for referring high risk patients to tertiary centers for further diagnostics and highly specialized treatment. Further development of ROMA, where inclusion of US findings could be incorporated in the risk estimation is necessary, if the algorithm should play a significant role after admission.

ROMA could potentially shorten the time spend before OC patients reach a tertiary center. Further improvements of HE4 and ROMA as differential tools are still needed, especially regarding premenopausal women.

Conflict of interest statement

There are no conflicts of interest in this study.

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