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REVIEW

The impact of micronized progesterone on breast cancer risk: a systematic review

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ABSTRACT

Postmenopausal women with an intact uterus using estrogen therapy should receive a progestogen for endometrial protection. The debate on bioidentical hormones including micronized progesterone has increased in recent years. Based on a systematic literature review on the impact of menopausal hormone therapy (MHT) containing micronized progesterone on the mammary gland, an international expert panel's recommendations are as follows: (1) estrogens combined with oral (approved) or vaginal (off-label use) micronized progesterone do not increase breast cancer risk for up to 5 years of treatment duration; (2) there is limited evidence that estrogens combined with oral micronized progesterone applied for more than 5 years are associated with an increased breast cancer risk; and (3) counseling on combined MHT should cover breast cancer risk – regardless of the progestogen chosen. Yet, women should also be counseled on other modifiable and non-modifiable breast cancer risk factors in order to balance the impact of combined MHT on the breast.

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Micronized progesterone; breast density; breast biopsy; breast cancer risk; menopause; combined estrogen–progestogen therapy; hormone therapy

Introduction

The steroid hormone progesterone (P) plays a key role in female reproduction[1]. For therapeutic reasons, micronized progesterone (MP) can be used, for example, for endometrial protection when estrogens are applied in menopausal women with an intact uterus[2]. To discuss various topics on MP, regular international expert meetings of three gynecological endocrinologists from the German-speaking countries, Austria, Germany and Switzerland, have been held since 2015 aiming to provide scientifically proven statements on MP treatment in peri- and postmenopausal women, based on a systematic literature search and discussion of the results. The impact of estrogens combined with MP on the mammary gland, especially on breast density, biopsies (benign breast tissue) and cancer risk is the second topic of this series[3].

Material and methods

In May 2016, a systematic literature search was performed by an independent agency (gwd consult) using the databases Medline (Pubmed) and Embase. Only articles in English were included. There was no time restriction applied. For each topic (impact of MP on (1) breast biopsy, (2) breast histology and (3) breast cancer risk), individual searches were performed using multiple combinations of keywords, Mesh-terms and text words related to the respective topic. For the first topic, included keywords were 'progesterone', 'breast', 'density', 'treatment', 'micronized', 'mammography', 'exogenous', 'hormone', 'proliferation', 'HRT', 'bio-identical', while 'MPA', 'norethisterone', 'progestin', 'medroxyprogesterone' and 'receptor' were excluded keywords. The search yielded 60 relevant articles. For the second topic, included keywords were 'progesterone', 'histologic', 'treatment', 'breast', 'hormone', 'biopsy', 'parenchymal', 'bio-identical' and 'histology' and excluded keywords were 'progestin', 'medroxyprogesterone', 'norethisterone' and 'receptor". The search yielded 30 relevant articles. For the third topic, included keywords were 'progesterone', 'breast', 'cancer', 'risk', 'treatment', 'micronized', 'bio-identical' while excluded keywords included 'receptor' and 'progestin". The search yielded 83 relevant articles. After exclusion of duplicates, the final list of relevant articles comprised 141 out of all relevant 173 articles. After May 2016, five additional articles have been identified and included into the review[4–8]. The final eligibility assessment and evaluation of the studies' quality were performed by the expert group (PS, JN, LW).

Results

Of 143 hits, 19 studies[4–22] were selected for the systematic review and expert panel's discussion. The other publications were excluded as they, for example, did not use MP but synthetic progestins although stated otherwise in the title, focused on infertility treatment or were not original articles,

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respectively. In the following, the term 'progestogen' was used as an umbrella term for MP and synthetic progestins.

Breast density

Of 60 hits, only six articles were suitable for this review[9–14] (Table 1). Of those, four were subgroup analyses of the placebo-controlled, randomized-controlled trial (PC-RCT) Postmenopausal Estrogen/Progestin Intervention (PEPI) trial[9–12], one was a *post-hoc* analysis of two PC-RCTs[13] and another one a head-to-head RCT[14]. Sample size ranged from 77[14] to 571[10] postmenopausal women. Treatment duration ranged from 2 months[14] to 3 years[9]. Within the PEPI trial, four menopausal hormone therapy (MHT) regimens were compared to placebo[9–12]. MHT regimens comprised oral conjugated equine estrogens (CEE) at 0.625 mg/day (o-CEE), o-CEE at 0.625 mg/day combined with oral medroxyprogesterone acetate (o-MPA) at 10 mg/day for 12 days per month (o-CEE + o-seqMPA), o-CEE at 0.625 mg/day combined with o-MPA at 2.5 mg/day (o-CEE + o-contMPA), and o-CEE at 0.625 mg/day combined with oral MP (o-MP) at 200 mg/day for 12 days per month (o-CEE + o-contMP). *The post-hoc* analysis combined two Danish RCTs[13] comparing placebo to either an oral MHT or nasal–oral MHT regimen. The oral MHT regimen contained oral 17β-estradiol (o-E2) at 1 mg/day combined with trimegestone at 0.125 mg/day (o-E2 + o-contTrimegestone), whereas the nasal–oral MHT contained either nasal E2 at 150 or 300 μg/day, respectively, combined with o-MP at 200 mg/day for 14 days per month in women with an intact uterus (n-E2 ± o-seqMP). The head-to-head RCT[14] used two different MHT regimes containing either o-CEE at 0.625 mg/day sequentially combined with o-MPA at 5 mg/day (o-CEE + o-seqMPA) or transdermal E2 (t-E2) gel at 1.5 mg/day sequentially combined with o-MP at 200 mg/day (t-E2 + o-seqMP).

Mammographic density was assessed either categorically, e.g. by Breast Imaging Reporting and Data System (BI-RADS) grades[9,13,14], or continuously, e.g. by computer-based mammographic percent density[10–13]. After 1 year of MHT within the PEPI trial, mammographic density was significantly increased by all estrogen–progestogen regimens but not by o-CEE or placebo[9–11]. There were no group differences between combined MHT regimens[9–11]. All mammographic density increases observed comprised only one category and mostly appeared during the first year of MHT use[9]. Similarly, mammographic density was significantly increased by oral estrogens combined with trimegestone[13] or MPA[14]. In contrast, mammographic density remained unchanged after treatment with oral or nasal estrogens combined with o-MP[13,14]. Furthermore, the associations between mammographic density and new-onset breast discomfort[11], change in serum progestogen levels or progesterone receptor genotype[12] were analyzed. Women with new-onset breast discomfort had a 3.9% increase in mammographic density regardless of MHT type[11]. Increases of serum progestogen in the highest quartile were associated with 3.5% higher mammographic density compared to increases in the lowest quartile. However, there was no indication that genetic variations in the progesterone receptor had an impact on mammographic density or modified the impact of serum progestogen levels on mammographic density[12].

Breast biopsy

Of 30 hits, only three studies were prospective randomized intervention trials[14–17], of which one study used o-MP[14,15] and two topical (applied directly on the breast) MP[16,17], respectively (Table 2). The latter two trials[16,17] were both placebo-controlled with three active comparator arms: topical MP 25 mg/day, topical E2 gel 1.5 mg/day, and the combination of both (E2 + MP). Study duration was short and comprised 11–14 days prior to a scheduled surgery for the removal of a breast lump. The cohorts included either 33 premenopausal[16] or 40 postmenopausal women[17]. The study endpoints were similar, namely serum steroid levels (E2, P), tissue steroid concentration (E2, P), mammary epithelial mitotic index and cell proliferation marker (PCNA) expression. While serum E2 levels were significantly higher in women applying topical E2 compared to those applying MP or placebo, significant group differences for serum P levels were only found in postmenopausal[17] but not in premenopausal topical MP users[16]. Tissue E2 concentration was significantly higher in women applying topical E2 compared to those applying placebo[16,17] or MP[17]. Tissue P concentration was significantly higher in women applying topical MP compared to placebo[16] or did not reveal any group differences[17]. Mammary epithelial mitotic index was significantly increased in those women applying topical E2 when compared to those using topical MP[16,17], E2 + MP or placebo[17]. Similarly, PCNA expression was highest in topical E2 users[16,17] but still significantly higher in women applying topical E2 + MP compared to women applying MP[16] and placebo[17]. Both authors came to the conclusion that topical MP for up to 14 days reduced E2-induced mammary epithelial proliferation.

The impact of a 2-month systemic MHT containing MP on the mammary gland in 77 healthy postmenopausal women was investigated by one RCT yielding three publications[14,15]. In this RCT, head-to-head comparisons were performed using two different MHT regimes containing either o-CEE at 0.625 mg/day sequentially combined with o-MPA at 5 mg/day (o-CEE + o-seqMPA) or t-E2 gel at 1.5 mg/day sequentially combined with o-MP at 200 mg/day (t-E2 + o-seqMP). Core needle biopsy of the upper outer quadrant of the left breast was performed at baseline and study end. Study endpoints were breast cell proliferation (Ki-67/MIB-1) and apoptosis (bcl-2) assessed by immunohistochemistry[14,15], single gene expression analysis assessed by reverse transcription polymerase chain reaction (rtPCR)[14] and whole genome expression analysis by microarray[14]. Assessable breast samples at both time points were available for 10%[14] to 49%[14,15] of subjects. After 2 months of treatment, breast cell proliferation and Ki-67 gene expression were significantly increased by o-CEE + o-MPA but not by t-E2 + o-MP[14,15]. In contrast, breast cell apoptosis and bcl-2 gene expression were either decreased by t-E2 + o-MP or did not reveal group differences[14,15]. Induction of progesterone receptor B expression was slightly but not significantly lower after t-E2 + o-MP than o-CEE + o-MPA treatment[14]. Microarray analysis revealed an

Table 1. Overview of trials investigating menopausal hormone therapy (MHT) containing micronized progesterone (MP) and breast density.

Author (year)	*Study design*	*Sample size, mean age (years) and BMI (kg/m^2) of the participants*	*Study duration*	*Treatment arms: Dosage and application regimen*	*Breast density assessment*	*Change in mammographic density*
Greendale (1999)[9]	PC-RCT (PEPI substudy)	307 postmenopausal women, age 59.2 ± 4.2, BMI 27.1 ± 4.9	3 years	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV: o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	BI-RADS grades	% of women whose MD increased by at least one BI-RADS grade from baseline to 12 months: I. CEE 3.5 (95% CI 1.0–12.0); II. CEE + seqMPA 23.5 (95% CI 11.9–35.1); III. CEE + conMPA 19.4 (95% CI 9.9–28.9); IV. CEE + seqMP 16.4 (95% CI 6.6–26.2); V. Placebo 0.0 (95% CI 0.0–4.6); all MD increases were increases of one grade. Adjusted ORa for MD increase from baseline to 12 months: CEE vs. CEE + seqMPA OR 13.1 (95% CI 2.4–73.3; $p = 0.003$); CEE vs. CEE + conMPA OR 9.0 (95% CI 1.6–50.1; $p = 0.012$); CEE vs. CEE + seqMP OR 7.2 (95% CI 1.3–40.0; $p = 0.024$); no significant differences between EPT groups
Greendale (2003)[10]	PC-RCT (PEPI substudy)	571 postmenopausal women, age 56.0 ± 4.3, BMI 26.2 ± 4.5	12 months	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV: o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	Computer-assisted method	Mean change in mammographic percent density from baseline to 12 months[b]: V. Placebo −0.07% (95% CI −1.50–1.38%; p = n.s.); I. CEE 1.17% (95% CI -0.28–2.62%; $p = 0.241$); II. CEE + seqMPA 4.76% (95% CI 3.29–6.23%; $p \leq 0.001$); III. CEE + conMPA 4.58% (95% CI 3.19–5.97%; $p < 0.001$); IV. CEE + seqMP 3.08% (95% CI 1.65–4.51%; $p = 0.002$); no significant differences between EPT regimens
Crandall (2006)[11]	PC-RCT (PEPI substudy)	533 out of 875 postmenopausal women, age 56.1 ± 4.3, BMI 26.0 ± 4.5	12 months	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV: o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	Computer-assisted method	Mean 12-month change in percent breast density from baseline[c]: V. Placebo -0.4%; I. CEE 0.9% ($p = 0.25$); II. CEE + seqMPA 4.6% ($p = 0.003$); III. CEE + conMPA: 4.4% ($p < 0.001$); IV. CEE + seqMP 3.1% ($p < 0.001$); no significant differences between EPT regimens ($p = 0.68$); the demonstrated association between incident breast discomfort and increased percent breast density was similar in all active treatment arms
Pettersen (2008)[13]	*Post-hoc* analysis of two PC-RCTs	Nasal MHT trial: 267 postmenopausal women; oral MHT trial: 89 postmenopausal women	2 years	Nasal MHT trial: group 1, nasal E2 150 µg/day + MP 200 mg/day on 14 days/month (route of application not reported); group 2, nasal E2 300 µg/day + MP 200 mg/day on 14 days/month; group 3, placebo. Oral MHT trial: group 1, trimegestone 0.125 mg/day (+ calcium 500 mg/day + vitamin D 400 IU/day); group 2, placebo	BI-RADS grades; computer assisted methods	Nasal MHT trial: no significant difference between baseline and after 2 years, no difference between placebo and MHT Oral MHT trial: significant increase in EPT vs. baseline and placebo ($p < 0.05$)
Lee (2012)[12]	PC-RCT (PEPI substudy)	210 postmenopausal women randomized to EPT with baseline and at least one follow-up mammogram, serum samples at baseline and 12 months, age 56.1 ± 4.3, BMI 26.2 ± 4.5	12 months	I. o-CEE 0.625 mg/day; II. o-CEE 0.625 mg/day + o-MPA 10 mg/day for 12 days/month; III. o-CEE 0.625 mg/day + o-MPA 2.5 mg/day; IV. o-CEE 0.625 mg/day + o-MP 200 mg/day for 12 days/month; V. Placebo	Computer assisted method	In all EPT arms combined (II–IV), increases of serum progestogen in the highest quartile were associated with 3.5% higher MD ($p = 0.046$) compared to increases in lowest quartiled; no strong indication that genetic variations in PGR had an impact on MD or modified impact of serum progestogen levels

(*continued*)

Table 1. Continued

Author (year)	Study design	Sample size, mean age (years) and BMI (kg/m²) of the participants	Study duration	Treatment arms: Dosage and application regimen	Breast density assessment	Change in mammographic density
Murkes (2012)[14]	RCT	77 postmenopausal women, age 44–66 years, BMI 18–30	2 months	Group 1: o-CEE 0.625 mg/day + o-MPA 5 mg/day for 14 days per 28 days per cycle; Group 2: t-E2 gel 1.5 mg/day- + o-MP 200 mg/day for 14 days per 28 days per cycle	BI-RADS grades	BI-RADS grades increase of at least one BI-RADS grade: group 1, CEE + seqMPA 18.9% ($p = 0.01$); group 2, t-E2 + seqMP 6.3% (p = ns)

BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index; CEE, conjugated equine estrogens; con, continuously combined; E2, estradiol; EPT, estrogen–progestogen therapy; MD, mammographic breast density; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; MP, micronized progesterone; ns, non-significant; o, oral; OR, odds ratio; PC-RCT, placebo-controlled randomized trial; PGR, progesterone receptor; seq, sequentially combined; t, transdermal.

[a]Adjusted to baseline BI-RADS grade, age, cigarette smoking, alcohol use, clinical site, and uterus status; [b]p values for comparisons to placebo; adjusted to baseline mammographic percent density, age, (12-month change in) BMI, alcohol, smoking, physical activity, hysterectomy, clinic site; [c]unadjusted; p values for comparison to placebo; [d]adjusted to baseline mammographic percent density, age, (change in) BMI, race, smoking, alcohol, physical activity, parity, serum estrone level.

altered gene expression profile (fold change ≥1.5) for 2500 genes within the o-CEE + o-MPA arm and 300 genes within the t-E2 + o-MP arm[14]. A total of 225 genes were involved in mammary tumor development of which 198 were attributable to o-CEE + o-MPA and 34 to t-E2 + o-MP. The different aspects of the study came to the conclusion that, in comparison to 'conventional' MHT, transdermal E2 combined with oral MP induced less proliferation and adverse expression of important genes regulating proliferation, apoptosis and tumor inclination *in vivo*.

Breast cancer risk

Breast cancer risk in respect to MHT containing MP was assessed by two systematic reviews and meta-analysis[4,7], one retrospective cohort study[18], two prospective cohort studies (the Etude Epidémiologique de femmes e la Mutuelle Générale de l'Education Nationale (E3N), and Menopause: Risk of breast cancer, morbidity and prevalence (MISSION))[8,19–21,23,24], one case–control study (CECILE, a population-based case-control study in Cote d'Or and Ille-et-Vilaine)[25] and two PC-RCT (Kronos Early Estrogen Prevention Study (KEEPS)[22], and Early versus Late Intervention Trial with Estradiol (ELITE)[5]) (Table 3). The first meta-analysis[7] included two cohort studies[8,24] and reported that breast cancer risk was lower for estrogens combined with MP than with synthetic progestins (relative risk (RR) 0.67; 95% confidence interval (CI) 0.55–0.81). Mean MHT duration was 7.0 years[24] and 8.3 years[8], respectively. According to the second meta-analysis covering 14 trials, breast cancer risk was increased when estrogens were combined with MPA, norethisterone (NET) or levonorgestrel (LNG) but not when combined with dydrogesterone (DYD) or MP[4], respectively. However, the duration of MHT use was not considered.

Except for the two US-American PC-RCTs, all other studies were performed in France. The primary endpoints were breast cancer risk[8,18–21,23–25] or changes in carotid artery intima-media thickness[5,22]. In the latter, breast cancer was assessed as a serious adverse event[5,22]. The sample size ranged from 643[5] to 80 391[23] postmenopausal women, and mean follow-up from 4.0[22] to 11.2[21] years. At study entry, women were in their fifties in all[5,18–20,22–24] but two studies[5,8] that also recruited women during late postmenopause. Only CECILE did not report on participants' age[25]. Information on MHT use was obtained from medical records[8,18], self-administered questionnaires at baseline[26] and then every 2 years[19–21,23,24], in-person interviews[25], and scheduled visits at 2-month[5] or 12-month[22] intervals. Mean duration of MHT use ranged from 2.8 years[19] to ≥10 years[18]. Adherence to medication was high in KEEPS (>94%)[22] and ELITE (98%)[5] but not reported in the other studies included.

Both PC-RCTs, KEEPS[22] and ELITE[5] used a sequentially combined MHT. In KEEPS, o-CEE at 0.45 mg/day or t-E2 patch at 50 µg/day was combined with o-MP 200 mg/day on days 1–12 of each month (o-CEE + o-seqMP, t-E2 + o-seqMP)[22]. In ELITE, o-E2 at 1 mg/day was combined with vaginal MP at 45 mg/day (4% gel) on 10 days during each 30-day cycle (o-E2 + vag-seqMP)[5]. The observational cohort and case–control studies differentiated between progestogen types such as

Table 2. Overview of trials investigating menopausal hormone therapy (MHT) containing micronized progesterone (MP) and breast biopsies.

Author (year)	*Study design*	*Sample size (recruited/analyzed), age (years), BMI (kg/m^2)*	*Study duration*	*Treatment arms: dosage and application regimen*	*Breast biopsy*	*Results*
Chang (1995)[16]	PC-RCT	34/33 premenopausal women, age 18–45	11–13 days (start at CD 1)	I. Topical MP 25 mg/day; II. Topical E2 gel 1.5 mg/day; III. Topical E2 gel 1.5 mg/day + topical MP 25 mg/day; IV. Placebo	Surgery for removal of lump at CD 11–13 (macroscopically normal sample taken 1 cm away from the lump)	*Proliferation* Mitotic index = mitosis per 1000 cells: I. MP 0.17 ± 0.19; II. E2 0.83 ± 0.42 ($p < 0.05$ vs. I.); III. MP + E2 0.52 ± 0.42; IV. Placebo 0.51 ± 0.24 PCNA labeling index: I. MP 1.9 ± 0.5%; II. E2 17.4 ± 6.4% ($p < 0.05$ vs. IV); III. MP + E2 6.5 ± 4.4% ($p < 0.05$ vs. I.); IV. Placebo 7.8 ± 4.8%
Foidart (1998)[17]	PC-RCT	44/40 postmenopausal women, age 47–80, mean BMI 23.6–26.5	14 days	I. Topical MP 25 mg/day; II. Topical E2 gel 1.5 mg/day; III. Topical E2 gel 1.5 mg/day + topical MP 25 mg/day; IV. Placebo	Surgery for removal of lump on study day 15 (macroscopically normal sample taken 5 cm away from lump)	*Proliferation* Mitotic index = mitosis per 1000 cells: I. MP 0.19 ± 0.25; II. E2 0.6 ± 0.2 ($p < 0.05$ vs. group I, III and IV); III. 0.2 ± 0.15; IV. 0.15 ± 0.2 PCNA labeling index: I. MP 1.5 ± 0.6% ($p < 0.001$ vs. IV.); II. E2 11.5 ± 2.3% ($p < 0.001$ vs. I, III, IV); III. MP + E2 1.3 ± 1.1% ($p < 0.05$ vs. IV); IV. Placebo 0.1 ± 0.1%
Murkes (2011)[15], (2012)[14]	RCT	77/71 postmenopausal women, age 44–66, BMI 18–30	2 months	I. o-CEE 0.625 mg/day + o-MPA 5 mg/day for 14 days per cycle; II. t-E2 gel 1.5 mg/day + o-MP 200 mg/day for 14 days per cycle	Core needle biopsy (upper outer quadrant of left breast) at baseline and at end of second treatment cycle	*Proliferation* Mean Ki67/MIB positive cells (range in %): I. oCEE + o-seqMPA at baseline 1% (0–4), after 2 months 10% (0–56) ($p = 0.003$); II. t-E2 + o-seqMP at baseline 3.1% (0–21.5), after 2 months 5.8% (0–39) (n.s.) *Apoptosis* Mean Bcl-2-positive cells (range in %)[a]: I. o-CEE + o-seqMPA baseline 46% (0–90), after 2 months 27% (0–80) (n.s.); II. t-E2 + o-seqMP baseline 49% (0–100%), after 2 months 26% (0–80) ($p = 0.06$) *Microarray analysis* I. o-CEE + o-seqMPA: 2500 altered genes (fold change ≥1.5); II. t-E2 + o-seqMP: 300 altered genes (fold change ≥1.5); I + II. 300 commonly altered genes
Söderqvist (abstract)[6]	RCT in healthy postmenopausal women	77/8 (microarray) and 30 (rtPCR)	2 months	Group 1: o-MPA 5 mg/day on 14 days out of 28 days per cycle; group 2: o-MP 200 mg/day on 14 days out of 28 days per cycle	Group 1: o-CEE 0.625 mg/day; group 2: t-E2 gel 1.5 mg/day	*Microarray analysis* 225 genes involved in mammary tumor development (group 1: $n = 198$, group 2: $n = 34$); rtPCR: MKi-67: group 1 significant increase from baseline to study end (group 2 n.s.); PRL and bcl-2: group 2 significant decrease from baseline to study end (group 1 n.s.)

BMI, body mass index; CD, cycle day; CEE, conjugated equine estrogens; E2, estradiol; EPT, estrogen–progestogen therapy; MPA, medroxyprogesterone acetate; MP, micronized progesterone; n.s., non-significant; o, oral; PC, placebo-controlled; PCNA, proliferating cell nuclear antigen; PRL, prolactin; RCT, randomized controlled trial; rtPCR, reverse transcription polymerase chain reaction; seq, sequentially combined; t, transdermal.
[a]Results according to Murkes[15].

Table 3. Overview of trials investigating menopausal hormone therapy (MHT) containing micronized progesterone (MP) and breast cancer risk.

Author (year)	*Study design*	*Sample size; cohort characteristics*	*Study duration/ follow-up, duration of MHT use*	*Reproductive stage; age of participants*	*Progestogen dosage; application regimen*	*Estrogen dosage; application regimen*	*Endpoints*	*Results*
De Lignières (2002)[18]	Cohort study	3175 women with ≥1 year of follow-up; 1739 MHT users (systemic ET for ≥1 year), 1545 EPT users (89%)	Follow-up: mean 8.9 (range 1–24) years	Postmenopause (or ≥50 years); mean age 50 (range 20–59) years	MHT regimen and dosage not specified; EPT users: 58% MP, 10% DYD, 32% other progestogens (promegestone, lynestrenol, CMA, NOMAC, MPA) < 3%	Dosage not specified; EPT users: 83% t-E2 gel, 17% t-E2 patch, o-E2 or o-CEE	I. BC incidence during follow-up or since menopause; II. SIR; III. Relative risk for BC by Cox's proportional hazards regression; IV. Risk for BC according to duration of use	I. 105 women with BC (43 MHT nonusers, 59 EPT, 3 ET users); II. SIR (95% CI): nonuser 1, EPT 1.19 (0.81–1.79); III. RR[a] (95% CI): nonuser: 1, EPT 1.1 (0.73–1.66); IV: no significant increase in RR[b] with the duration of MHT use (≥10 years: RR 1.15 (95% CI 0.64–2.05))
Espié (2007)[8]	Prospective cohort study (MISSION)	4949 women; 2693 with MHT exposure (current systemic MHT use or MHT stop ≤5 years ago), 2256 with MHT non-exposure (never MHT use or stop >5 years ago), 31.2% MHT use >10 years	Mean follow-up 2.5 years; mean MHT duration 8.3 ± 5.3 years	Postmenopause; mean age 60.6 ± 6.3 years (MHT exposure) and 64.2 ± 8.3 years (MHT non-exposure)	MHT regimen and dosage not specified; EPT users: 43.7% MP, 56.3% synthetic progestogens (excluding MPA and 19-nortestosterone derivatives)	Dosage not specified; E2 alone 13.3%; ET and EPT: 77.7% t-E2, 22.3% o-E2	I. BC incidence; II. RR for BC compared with MHT non-exposure by Mann–Whitney test; III. RR according to MHT duration; IV. RR according to MHT type	I. 17/2662 women with BC in MHT-exposed group, 14/2004 women with BC in MHT non-exposed group; II. non-adjusted $RR_{exposed/non\text{-}exposed}$ 0.94 (95% CI 0.449–1.858); III. non-adjusted $RR_{\leq 5\ yrs\ >5yrs.}$ 1.23 (95% CI 0.45–3.35); IV. E2 alone: non-adjusted RR 0.40 (95% CI 0.05–3.00); E2 + synthetic progestogen non-adjusted RR 1.00 (95% CI 0.48–2.07); t-E2 + MP non-adjusted RR 1.07 (95% CI 0.50–2.27); o-E2 + synthetic progestogen non-adjusted RR 0.81 (95% CI 0.23–2.85)
Fournier (2005)[19]	Prospective cohort study (E3N)	54 548 women; 29 420 incident MHT users (systemic MHT ≥1 year but not prior to baseline)	Mean 5.8 (range 0.1–10.6) years; mean MHT duration 2.8 (range 2.4–3.1) years	Postmenopause; mean age 52.8 (range 40–66.1) years	MHT regimen and dosage not specified; main use[c] of oral progestogen in MHT users (EPT 83.3%): MP 20.1%, progesterone derivatives (retroprogesterone, pregnane, norpregnane derivatives) (main use 58.3%), testosterone derivatives) (main use 4.6%)	Dosage not specified; main use[c] of estrogens in MHT users: weak estrogens 4.5, CEE 1%, E2 93.2% (transdermal 59.9%)	I. BC incidence; II. RR for BC compared with MHT non-users by Cox's proportional hazards regression	I. 984 women with invasive BC; II. RR[d] (95% CI) compared with non-users: any MHT 1.2 (1.1–1.4), all EPT 1.3 (1.1–1.5), E2 + MP 0.9 (0.7–1.2), estrogens + synthetic progestogens 1.4 (1.2–1.7); III. No evidence of increasing risk with increasing duration of HRT exposure except for oral estrogens combined with synthetic progestogens (ns, $p = 0.07$)

(*continued*)

Table 3. Continued

Author (year)	Study design	Sample size; cohort characteristics	Study duration/ follow-up, duration of MHT use	Reproductive stage; age of participants	Progestogen dosage; application regimen	Estrogen dosage; application regimen	Endpoints	Results
Fournier (2008)[24]	Prospective cohort study (E3N)	80 377 women; 56 674 incident and prevalent MHT users; 23 703 MHT non-users	Mean 8.1 ± 3.9 years; mean MHT duration 7.0 ± 5.2 years	Postmenopause; mean age at MHT start 52.4 ± 4.6 years, mean age at follow-up start 53.1 (range 40–66.1) years	MHT regimen and dosage not specified; combined MHT using oral progestogen: MP, DYD, other progestogens = progesterone + testosterone derivatives	Dosage not specified; mainly oral and transdermal E2, 1.3% o-CEE	I. BC incidence; II. RR for BC compared with MHT non-users by Cox's proportional hazards regression	I. 2354 women with invasive BC; II. adjusted RR (95% CI): estrogen + MP 1.00 (0.83–1.11) (129 BC cases/40 537 person-years); estrogen + DYD 1.16 (0.94–1.43); for estrogen + other progestogens 1.69 (1.50–1.91 (527 BC cases/104 243 person-years); III. Significant trends of increased risk with increased duration of use of estrogen + MP and estrogen + other progestogens; IV. Risk of BC after treatment stopped: no significant increased BC risk for all EPT ≥2 years after last use
Fournier (2008)[23]	Prospective cohort study (E3N)	80 391 women; 2265 BC cases with histology; 1792 BC cases with hormone receptor status	Mean 8.1 ± 3.9 years	Postmenopause;mean age at follow-up start 53.1 (range 40–66.1) years	MHT regimen and dosage not specified; combined MHT using oral progestogen: MP, DYD, other progestogens (progesterone + testosterone derivatives)	Dosage not specified; mainly oral and transdermal E2, 1.3% o-CEE	I. BC histology (ductal, lobular, other); II. hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR-, missing); III. RR for BC histology by Cox's proportional hazards regression; IV. RR for BC hormone receptor status by Cox's proportional hazards regression	I. 1560 ductal and 448 lobular carcinoma; II. 1054 ER+/PR+, 372 ER+/PR-, 64 ER-/PR+, 302 ER-/PR-; III. adjusted RR (95% CI) estrogens + MP: ductal carcinoma 1.0 (0.8–1.3); lobular carcinoma 1.1 (0.7–1.7); estrogens + other progestogens: ductal carcinoma 1.6 (1.3–1.8), lobular carcinoma 2.0 (1.5–2.7); IV. adjusted RR (95% CI): estrogens + MP: ER+/PR+ 1.2 (0.9–1.5), ER+/PR- 0.8 (0.5–1.5), ER-/PR+ 0.9 (0.3–2.6), ER-/PR- 1.0 (0.6–1.7); estrogens + other progestogens: ER+/PR+ 1.8 (1.5–2.1), ER+/PR- 2.6 (1.9–3.5), ER-/PR+ 1.0 (0.5–2.1) and ER-/PR- 1.4 (0.9–2.0)
Fournier (2009)[20]	Prospective cohort study (E3N)	53 310 women; 21 232 MHT never users; 26 171 MHT ever users with gap time ≤3 years; 5908 MHT ever users with gap time >3 years	Mean 8.1 ± 3.9 years	Postmenopause; mean age at follow-up start 54.6 ± 4.5 years	MHT regimen and dosage not specified; combined MHT using an oral progestogen: MP, DYD, other progestogens = progesterone + testosterone derivatives; recent MHT = current use and use within the previous 12 months	Dosage not specified; mainly oral and transdermal E2, 1.3% o-CEE	I. BC incidence; II. HRs for BC by Cox's proportional hazards regression comparing time from menopause (gap time) ≤ 3 years and >3 years and partially duration of use	I. 1726 women with invasive BC; II. adjusted HR (95% CI)[e]: recent EPT use: gap time ≤3 years: 1.61 (1.43–1.81), gap time >3 years: 1.35 (1.13–1.63); estrogen + MP: gap time ≤3 years significantly increased BC risk when used for >5 years (p trend for duration = 0.002), gap time >3 years did not increase BC risk regardless of duration of use (≤2 to >10 years) (p trend for duration = 0.54); estrogen + other progestogen:

(*continued*)

Table 3. Continued

Author (year)	Study design	Sample size; cohort characteristics	Study duration/ follow-up, duration of MHT use	Reproductive stage; age of participants	Progestogen dosage; application regimen	Estrogen dosage; application regimen	Endpoints	Results
								gap time ≤3 years significantly increased BC risk regardless of duration of use (≤2 to >10 years) (p trend for duration = 0.18), gap time >3 years significantly increased BC risk when used for >2 to ≤10 years (p trend for duration = 0.27)
Fournier (2014)[21]	Prospective cohort study (E3N)	78 353 women; 21 601 MHT never users; 31 223 MHT past users (no MHT in preceding 3 months); 17 986 MHT current users,	Mean 11.2 years	Postmenopause; mean age at end of follow-up 67.1 ± 7.8 years (MHT never users), 67.0 ± 5.8 years (MHT past users), 63.1 ± 5.5 years (MHT current users)	MHT regimen and dosage not specified; combined MHT using oral progestogen: MP, DYD, other progestogens = progesterone + testosterone derivatives, tibolone	Dosage not specified; mainly oral and transdermal E2	I. BC incidence; II. HRs for BC by Cox's proportional hazards regression with respect to time since last use and comparing short-term MHT use (≤5 years) with long-term MHT use (>5 years)	I. 3678 women with invasive BC; II. adjusted HR (95% CI): current estrogen + MP/DYD: ≤5 years 1.13 (0.99–1.29), >5 years 1.31 (1.15–1.48), any past use, ns effect on BC risk; current estrogen + other progestogen: ≤5 years 1.70 (1.50–1.91), >5 years 2.02 (1.81–2.26); stop of treatment after short-term use: ns effect; long-term-use: significantly elevated BC risk up to 10 years
Cordina-Duverger (2013)[25]	Population-based case-control study (CECILE)	1555 women; 739 BC cases, 816 controls	–	Postmenopause; range 35–74 years (82.3% of women between 55 and 74 years)	MHT regimen and dosage not specified; combined MHT MP, progesterone derivatives, testosterone derivatives, tibolone	Type of estrogens not further specified; dosage not specified	Invasive and *in situ* BC risk in comparison to MHT non-user by unconditional logistic regression analysis with regard to duration of use	Adjusted OR[f] (95% CI), estrogens + MP: any duration 0.80 (0.44–1.43) (25 cases/34 controls), <4 years 0.69 (0.29–1.68), ≥4 years 0.79 (0.37–1.71); estrogens + synthetic progestogens: any duration 1.72 (1.11–2.65) (67 cases/48 controls), <4 years 1.17 (0.48–2.86), ≥4 years 2.07 (1.26–3.39)
Harman (2014)[22]	PC-RCT (KEEPS)	727 randomized women (79% never MHT use before)	48 months; mean MHT use: o-CEE 37.4 ± 16.6 months, t-E2 34.6 ± 18.3 months, placebo 37.6 ± 17.3 months	Postmenopause; mean age at study entry 52.7 (range 42–58) years	Oral MP 200 mg/day on days 1–12 of each month (all women with estrogens)	o-CEE 0.45 mg/day or t-E2 50 µg/day	Primary endpoint: annual change in CIMT; BC as adverse event (annual mammogram)	BC as adverse events: $n = 3$ o-CEE, $n = 3$ t-E2, $n = 2$ placebo
Hodis (2016)[5]	PC-RCT (ELITE)	643 randomized women; 271 early postmenopause (previous MHT use 49–53%); 372 late postmenopause (previous MHT use 85–90%)	Median 4.8 (range 0.5–6.7) years	Postmenopause; median age at study entry 55.4 years (early postmenopause) and 63.6 years (late postmenopause)	Vaginal MP 45 mg/day (4% gel) on 10 days during each 30-day cycle or placebo (only in women with intact uterus receiving estrogens)	o-E2 1 mg/day or placebo	Primary endpoint: rate of change in CIMT; BC as adverse event	BC as adverse events: $n = 10$ o-E2, $n = 8$ placebo

(*continued*)

Table 3. Continued

Author (year)	Study design	Sample size; cohort characteristics	Study duration/ follow-up, duration of MHT use	Reproductive stage; age of participants	Progestogen dosage; application regimen	Estrogen dosage; application regimen	Endpoints	Results
Asi (2016)[7]	Systematic review and meta-analysis (2 cohort studies[8,24]	86 881 women	Mean follow-up 2.5 years[8] and 8.1 years[24]; mean MHT duration not given	Postmenopause; MHT exposed group: 60.6 ± 6.3 years, MHT non-exposed group: 64.2 ± 8.3 years[8]; MHT ever-use: 52.3 ± 4.1 years, MHT never-use 55.0 ± 4.8 years[24]	Dosage and route of administration not specified	Dosage and route of administration not specified	Relative risk for BC	RR 0.67 (95% CI 0.55–0.81)
Yang (2017)[4]	Systematic review and meta-analysis (14 trials; 5 RCT, 6 cohort studies, 2 nested case-control studies, 1 case-control study) including 9 with combined MHT	14 475 women	Not given	Peri- and postmenopausal women (not further specified)	Dosage and route of administration not specified: MPA, NETA, LNG, DYD, MP	Not further specified	Odds ratio for BC	OR (95% CI): All EPT 1.48 (1.30–1.68); ET + MPA 1.19 (1.07–1.33); ET + NETA 1.44 (1.26–1.65); ET + LNG 1.47 (1.17–1.85); ET + DYD 1.10 (0.89–1.36); ET + MP 1.00 (0.83–1.20)

BC, breast cancer; CEE, conjugated equine estrogens; CI, confidence interval; CIMT, carotid artery intima-media thickness; CMA, chlormadinone acetate; DYD, dydrogesterone; E2, estradiol; EPT, estrogen–progestogen therapy; ER, estrogen receptor; ET, estrogen therapy; HR, hazard ratio; LNG, levonorgestrel; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; MP, micronized progesterone; NETA, norethisterone acetate; ns, non-significant; NOMAC, nomegestrol acetate; o, oral; OR, odds ratio; PC, placebo-controlled; PR, progesterone receptor; RCT, randomized controlled trial; RR, relative risk; SIR, standardized incidence ratio = ratio of observed to expected number of BC; t, transdermal.

[a]Adjusted to period of treatment, date of birth and age at menopause; [b]Cox's proportional hazard risk model, using MHT use as time-dependent variable, stratified on period of treatment, date of birth and age of menopause; [c]'main use' corresponds to the MHT used for the greatest length of time; [d]adjusted for time since menopause, body mass index, age at menopause, parity and age at first full-term pregnancy, familial history of breast cancer, personal history of benign breast disease, use of oral progestogens before menopause, ever use of oral contraceptives, previous mammography; [e]adjusted for age and age at menopause. Further stratified on year of birth. In analyses according to type of recent EP-MHT, models are additionally adjusted for past use of estrogen + progesterone, estrogen + other progestogens; [f]adjusted for study area, age at reference date, age at menarche, parity, age at first full-term pregnancy, breast feeding, history of benign breast disease, family history of breast cancer in first-degree relatives, body mass index, oral contraceptive use.

MP[8,18–21,23–25], DYD[18,20,21,23,24] and synthetic progestins (progesterone- and testosterone derivatives)[8,18,19,21,23–25] but not between estrogen types, MHT dosages and MHT regimen (sequentially or continuously combined MHT). The definition of current and past MHT use differed between studies. For some, current MHT use corresponded to systemic estrogen therapy for ≥1 year[18–20,24]. For others, current systemic MHT also comprised women that had stopped MHT use ≤1 year[25] or even ≤5 years[8] before the reference date, which in contrast was defined as past use in another study[21]. One study grouped current and past MHT use together[23].

The first study to report on the impact of different progestogen types within combined MHT on breast cancer risk did not find a significant difference between combined MHT use and non-use (adjusted RR 1.10; 95% CI 0.73–1.66)[18]. This finding was not altered when differentiating between time since last MHT use (<5 years vs. ≥5 years) and duration of MHT use (<5 years vs. ≥ 5 years). Unfortunately, subgroup analysis for progestogen types was not performed. However, the majority of combined MHT contained MP (58%) or DYD (10%) and only <3% MPA. The MISSION trial did not find a significant difference for breast cancer risk when comparing MHT users with non-users (non-adjusted RR 0.91; 95% CI 0.45–1.86)[8]. Similarly, breast cancer risk in MHT users did not differ between MHT types and duration of use (≤5 years vs. >5 years). In contrast, when compared to MHT non-use, the first E3N report from 2005 found a significant increased breast cancer risk for any combined MHT use (multivariate adjusted RR 1.3; 95% CI 1.1–1.5)[19]. Breast cancer risk was not altered by duration of MHT use (<2 years vs. 2–4 years vs. ≥4 years; p for trend = 0.7). However, when differentiating for progestogen type, estrogens combined with oral MP were not associated with an increased breast cancer risk (multivariate adjusted RR 0.9; 95% CI 0.7–1.2), while estrogens combined with synthetic progestins were (multivariate adjusted RR 1.4; 95% CI 1.2–1.7). Duration of MHT use (<2 years vs. 2–4 years vs. ≥4 years) only had a slight impact when oral estrogens were combined with synthetic progestins (p for trend = 0.07) but not when combined with MP (p for trend = 0.9). Similarly, the second E3N report published in 2008 did not find an increased breast cancer risk for combined MHT containing either MP or DYD regardless of MHT duration (<2 years vs. 2–<4 years vs. ≥4–<6 years vs. ≥6 years), although a significant time trend was observed in women using estrogens combined with MP (p for trend = 0.04)[24]. In addition, combined MHT containing MP was not found to be associated with any breast cancer subtype[23]. These findings were supported by CECILE[25]. However, the numbers of cases and controls were very small in subgroups and the authors did not differentiate between invasive and *in situ* breast cancer. In contrast, the third E3N report from 2014 found a significant increased breast cancer risk for mean 6.1 years of use of combined MHT containing MP or DYD (multivariate adjusted RR 1.22; 95% CI 1.11–1.35). When differentiating between short-term (≤5 years) and long-term use (>5 years), a significant increased breast cancer risk was only found for long-term use (multivariate adjusted RR 1.31; 95% CI 1.15–1.48). In comparison, use of combined MHT containing synthetic progestogens for more than 5 years was associated with an increased breast cancer risk (multivariate adjusted RR 1.98; 95% CI 1.73–2.26). Importantly, after stopping MHT containing MP or DYD after >5 years of use, breast cancer risk dissolved immediately (3 months to 5 years since last use: multivariate adjusted RR 1.15; 95% CI 0.93–1.42). In contrast, breast cancer risk was still elevated even 5–10 years after stopping MHT containing synthetic progestins when use was at least 5 years (multivariate adjusted RR 1.34; 95% CI 1.04–1.73). The time gap between menopause and MHT initiation did not have an impact on breast cancer risk in women using estrogens combined with MP[20,21]. In the two PC-RCTs, breast cancer was newly diagnosed in eight women in KEEPS[22] (n = 3 o-CEE, n = 3 t-E2, n = 2 placebo), and in 18 women in ELITE[5] (n = 10 o-E2, n = 8 placebo), respectively. The difference between MHT and placebo groups was not significant in both studies.

Discussion

Current international guidelines on MHT recommend to combine a progestogen when using estrogen therapy in peri- and postmenopausal women with an intact uterus for endometrial protection[2,27–29]. However, long-term combined estrogen–progestogen therapy has been shown to be associated with an increased breast cancer risk. During the last years, the debate about (compounded) bioidentical hormones has increased tremendously[30–32]. Specifically, the question has been raised whether bioidentical hormone therapy including MP has a different or even beneficial impact on the mammary gland. Internationally, systemic MP is available at different dosages and routes of application. Also, indication and approval by regulatory authorities may differ from country to country. In Europe, systemic MP is available as a capsule (100 mg, 200 mg) for vaginal or oral application or as a vaginal gel (8% corresponding to 90 mg).

Our systematic review on the impact of estrogens combined with MP on the postmenopausal mammary gland showed that (1) mammographic density may either increase or remain unchanged, (2) proliferation induction was less pronounced compared to 'conventional' MHT, and (3) breast cancer risk was not affected for up to 5 years of treatment. However, (4) estrogens combined with MP or dydrogesterone were associated with a slight but significant increase in breast cancer risk after an average of 6 years of treatment duration.

Breast density is a mammographic finding based on differing proportions of fat, connective and epithelial tissue. Mammographic density can be assessed either by the BI-RADS classification (almost entirely fatty, scattered areas of fibroglandular density, heterogeneously dense, extremely dense)[33] or by more objective, but not widely implemented computer-based breast density assessments[34–36]. Mammographically dense breast tissue both decreases the sensitivity of mammograms and increases breast cancer risk[37] but not breast cancer mortality[38]. There are multiple factors contributing to mammographic density such as age, genetics, body habitus, parity, and MHT use. Our systematic review revealed contradicting results for MHT containing MP, with

two studies showing no change[13,14] and three substudies showing a significant increase in mammographic density[9–11]. The latter are in line with another longitudinal study showing that the age-related change from dense to fatty breast tissue was slowed down more in women taking combined MHT than in those taking estrogen alone[39]. The differing results may also be due to the method itself and differences between the US-American[4–6] and European[13,14] cohorts. US-American women were in their late fifties, overweight and had mostly used MHT before[4–6], while European women were younger at least in one substudy[13] and had a normal body mass index[8,9]. Baseline mammographic density was reported by all but one study[14]. Most women (approximately 60%) fell into the BI-RADS categories 1 and 2[9–11,13]. However, mammographic density interpretation is subjective to some degree as moderate interobserver and intraobserver variabilities, especially between the BI-RADS categories of heterogeneously dense and scattered areas of fibroglandular density, have been reported[40–42]. Accordingly, a striking but non-significant interobserver variability was reported by one study[9].

Due to heterogeneous study designs, reports on the impact of estrogens combined with MP on breast tissue were not comparable. Outcome markers differed, ranging from tissue sex steroid concentrations, immunohistochemistry, rtPCR to microarray gene expression analysis. Study duration was short and 2 months at maximum. Furthermore, two studies used topical MP[16,17] which is not thought to have a systemic impact[43]. The observed differences in tissue E2 and P concentrations may be due to pharmacological interference and different reproductive stages. Thus, there is only some weak evidence from breast biopsies in healthy women showing that estrogens combined with oral MP are more 'breast friendly' than estrogens combined with oral MPA, a finding supported by studies in non-human primates[44,45].

In respect to breast cancer risk, all studies confirmed that estrogens combined with MP did not increase breast cancer risk when treatment duration was 5 years or less. The only two studies assessing breast cancer risk in women using MHT containing MP for more than 5 years are the prospective cohort studies E3N and MISSION. Yet, compliance, dosage and route of application of MP were not exactly known. In addition, the E3N report from 2014 did not differentiate between MP and dydrogesterone. Another limitation of E3N was the high rates of MHT changes over time: of those who ever used estrogens combined with MP or dydrogesterone, 57% also used estrogens combined with synthetic progestogens[21]. The majority of studies used oral MP, which is the approved way of application for MHT. Thus, breast safety data on vaginal MP is scarce[5] or completely lacking for transdermal MP. Despite the limited evidence, women should be counseled that, if using combined MHT for more than 5 years, the risk of being diagnosed with breast cancer increases – regardless of the progestogen type chosen. However, in order to balance the impact of non-modifiable (e.g. genetics, breast density, parity) and modifiable breast cancer risk factors (e.g. alcohol, smoking, overweight/obesity, physical inactivity, MHT), women should also be counseled that the possible increased breast cancer risk with combined MHT is small (<1 per 1000 women per year of use) and lower than the increased risks associated with common lifestyle factors such as reduced physical activity, obesity and alcohol consumption[46].

Conclusion

Postmenopausal women with an intact uterus using estrogen therapy should receive a progestogen for endometrial protection. Based on a systematic literature review on the impact of micronized progesterone on the mammary gland, an international expert panel's recommendations on MHT containing micronized progesterone are as follows: (1) estrogens combined with oral (approved) or vaginal (off-label use) micronized progesterone do not increase breast cancer risk for up to 5 years of treatment duration; (2) there is limited evidence that estrogens combined with oral micronized progesterone applied for more than 5 years are associated with an increased breast cancer risk; and (3) counseling on combined MHT should cover breast cancer risk – regardless of the progestogen chosen. Yet, women should also be counseled on other modifiable and non-modifiable breast cancer risk factors in order to balance the impact of combined MHT on the breast.

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