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# Menopausal hormone therapy and breast cancer risk

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This narrative review analyses the customization of Menopause Hormone Therapy in the context of breast cancer risk in women with premature ovarian insufficiency (POI) and with menopause at a normal age. Women with Idiopathic POI, FMR-1 premutation or Turner syndrome, if left untreated, may have lower breast cancer risk compared to the healthy age-matched female population. These women should be treated with MHT until the age of 50, as the risk of breast cancer is equal to that of normally menstruating women. Carriers of BRCA 1 & 2 mutation after risk-reducing bilateral salpingo-oophorectomy (RRSO), without a personal history of cancer, have an increased breast cancer risk, but may probably be treated with MHT till the age of 50. POI resulting from endometriosis or cancer related treatment is discussed in a separate paper in this issue.

In peri- and postmenopausal women with menopausal symptoms and/or risk factors for osteoporosis in need of MHT, the individual breast cancer risk can be evaluated using internet-based calculators. In most women the 5-year-breast cancer risk is low (<3%) and MHT is a safe option. MHT should be prescribed with caution in women who have an intermediate risk (3–6%) and should not be prescribed in those who have a high risk of breast cancer (>6%). Oestrogen-only MHT and oestrogen-progestogen MHT containing

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micronized progesterone or dydrogesterone are associated with lower breast cancer risk compared to other combined MHT regimens.

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## Introduction

The term "Hormone replacement therapy" in the context of "menopause" emerged in the eighties. The first Women's Health Initiative (WHI) publications modified dramatically the paradigm of prescribing oestrogen and progestins after menopause [1]. Since then, other terms emerged, such as 'menopause hormone therapy (MHT) and Postmenopausal Hormone Therapy (PMHT) [1]. In the context of young patients with premature ovarian insufficiency (POI), the term Hormone Replacement Therapy (HRT) may however be more appropriate and is still used by many authors. Nevertheless, in this article, we will use the term MHT as it is the most used nowadays.

The ESHRE guidelines recommend that women with POI should be informed that MHT has not been found to increase the risk of breast cancer before the age of natural menopause and in a comprehensive review, a year later, the same authors confirm the absence of increased breast cancer risk in these patients [2,3]. In both papers, only a few articles are cited [4–8]. ACOG issued a committee opinion concluding that data from postmenopausal women should not be extrapolated to POI patients, since the latter are much younger and have a lower baseline risk [9]. It is further considered that BRCA 1 and 2 patients may be treated for a short term [9]. Only one article related to MHT is cited [10]. The others referenced articles concerned hormonal contraception [9].

The paucity of information prompted the following study questions:

1. Do POI patients run a different breast cancer risk than other women?
2. Does MHT increase breast cancer risk in POI patients?

We analysed these questions in relation to the following POI aetiologies: Idiopathic POI and POI associated with a genetic disease such as Turner—or fragile-X syndromes (FMR-1 premutation) and POI following risk-reducing surgery by bilateral salpingo-oophorectomy (RRSO), encountered in patients with BRCA 1 and 2 mutations. We did, however, not include in this review POI linked to infertility disorders such as endometriosis, POI following chemo- or radiation therapy for non hormone-sensitive cancer, survivors of childhood cancers and POI after hormone-sensitive cancer (Breast-, ovarian- and uterine cancer) since these subjects are discussed in separate chapter of this special issue.

The second part of this article focuses on the breast cancer risk evaluation of peri- and postmenopausal women considering a hierarchy of risk factors for breast cancer. We will discuss how to assess breast cancer risk using internet-based tools, when MHT is considered safe, when one should be cautious when prescribing MHT in a balanced decision shared with the patient and when MHT should rather be avoided.

## Breast cancer risk in women with POI and MHT

### *Idiopathic POI*

Benetti-Pinto et al. did not observe a breast density difference between 31 Brazilian POI patients, using MHT as compared to 31 age-matched menstruating women [4], and they confirmed later these results in a sample of 163 patients (n = 163) [5–7]. Wu et al. identified 1003 POI patients among 36,402 postmenopausal Chinese women, but only 93 POI patients were using baseline MHT. POI patients had more often a high waist-to-hip ratio (WHR), and an increased all-cause-mortality risk and cancer mortality, but no excess in breast cancer, which was reduced by 40% [8]. No information about the aetiology of POI was provided and there was on average, a gap of 24 years between menopause

occurrence and the baseline survey. No comparison was made between POI patients using or not MHT [8]. Ra et al. found an association between some breast cancer-related microRNA polymorphisms (G haplotype of miR-27a/miR-423/miR-608) and POI [11]. It is nevertheless unknown whether these data are of clinical significance. Women with primary ovarian insufficiency are much younger at the time of MHT initiation and their baseline risk of breast cancer is significantly lower compared with women who start MHT at the natural age of menopause, i.e., over 50 years. Consequently, most guidelines and opinion leaders suggest that POI patients should use MHT until the age 50–51 years [2,3,9,13] (Table I) (Fig. 1).

*Women with turner syndrome*

Schoemaker et al. and Viuff et al. reported respectively a 70% and 60% lower breast cancer risk among Turner patients, compiling data from the National Health Service Central Registers for England, Wales, and Scotland and the Danish National Patient Registry, although some other cancer risks were increased in these patients [14,15]. It remains unclear however, whether therapy for more than four decades is safe, although some small series suggest it is [16]. The overall balance is in favour of MHT treatment at least until the age of natural menopause [17]. ESHRE, ACOG, IMS and EMAS concluded that girls and women with POI due to Turner Syndrome should be offered MHT throughout the normal reproductive lifespan [2,3,9,13] (Table 1) (Fig. 1).

*Women with FMR1 premutation (fragile X)*

Fragile X syndrome (FXS) is an X chromosome-linked disorder. This gene mutation is the most common inherited cause of congenital mental disability. It is caused by low or absent levels of a fragile X mental retardation protein (FMRP), due to a loss-of-function mutation in the fragile X mental retardation 1 (FMR1) gene, located at Xq27.3 [18].

Discordant reports have been published about a possible association between BRCA1 or 2 mutations and FMR1 gene mutations, which may be population-dependent [19]. Laitman et al. reported that BRCA mutation carriers in Israel exhibit a distinct CGG FMR1 repeat size pattern, which is, however, unlikely to be associated with POI [20]. There are no definite guidelines concerning MHT and breast cancer risk for patients with POI harbouring the FMR1 premutation. We suggest therefore that these patients should be treated with MHT until the age of natural menopause.

*Women with POI at risk of breast cancer*

*BRCA 1, 2 mutation carriers*

BRCA1 mutation carriers have an estimated risk of developing breast and ovarian cancer of 72% and 44% respectively by age 80, while BRCA2 mutation carriers have a risk of about 69% and 17% [21] (Table 2). Women with BRCA1 mutations are eligible for risk-reducing bilateral salpingo-oophorectomy (RRSO) between age 35 to 40, and those with BRCA2 around 40 years of age and upon completion of childbearing [21] (Table 2). This means that many BRCA 1 & 2 patients will undergo induced menopause at an earlier age, with consequently an increased cardiovascular and osteoporosis risk and a loss of quality of life. It is controversial whether MHT increases the breast cancer risk in BRCA mutation carriers after RRSO.

Breast cancers in women with BRCA1 mutations are usually hormone receptor-negative, while those in women with BRCA2 mutations are generally expressing oestrogen and progesterone receptors [21]. It is possible, therefore that the impact of MHT, starting also at different ages, varies. Nevertheless, many studies combine these two groups. Our literature appraisal retrieved several review articles and two recent meta-analyses and systematic reviews [21–24]. The review by Marchetti et al. [22] included three articles [10,25,26] and the review of Gordhandas et al. [25] discussed four articles [10,26–28]. Marchetti et al. conducted a meta-analysis of three cohorts including in total 1100 carriers of BRCA1 or BRCA2 mutations who underwent RRSO [10,25,26], and concluded that MHT users had no increased breast cancer risk as compared to non-MHT users. They reported however that estrogen-only therapy (ET) is associated with a lower BC risk as compared to estrogen-progestin therapy (EPT) [22].

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**Table 1**
Breast cancer risk in relation to POI aetiology and MHT (IA: Non-Cancer related, IB: Patients at increased cancer risk).

| a | Breast cancer risk | Risk using MHT | Benefit-risk balance of MHT | Duration | Level of evidence (endorsed by guidelines) |
|---|---|---|---|---|---|
| **IA. Non-cancer related cause** | | | | | |
| Idiopathic | Unknown | Probably only moderate added risk | In favour of MHT | Throughout the normal reproductive lifespan | C (EHRE<br>ACOG<br>IMS<br>EMAS) |
| Turner syndrome | Possibly reduced | Probably no or only moderate added risk | In favour of MHT | Throughout the normal reproductive lifespan | C (ESHRE<br>IMS, EMAS) |
| Fragile X or FMR1 premutation | Unknown | Probably no or only moderate added risk | In favour of MHT | Throughout the normal reproductive lifespan | GPP |
| **IB. Patients at increased cancer risk** | | | | | |
| Mutated BRCA 1 & 2 patients after RRSO without personal history of a cancer | Increased but less after RRSO | Unchanged or minimally increased | In favour of MHT | Throughout the normal reproductive lifespan | C (ESHRE)<br>SGO<br>NAMS<br>IMS<br>EMAS |
| Lynch Syndrome | Uknown | Unchanged or minimally increased | In favour of MHT | Throughout the normal reproductive lifespan | GPP |

The grade of a recommendation reflects the strength of the evidence supporting it. Grade A indicates that the recommendation is based on a high-quality systematic review or multiple randomized controlled trials (RCTs), Grade B recommendations are based on a single RCT or a large trial or study of high quality, Grade C on moderate quality trials or studies and Grade D on at least moderate quality non-analytical studies. GPP: Expert opinion [2]. POI: Premature Ovarian Insufficiency, MHT: Menopause Hormone Therapy, RRSO: Risk-reducing-bilateral-salpingo-oophorectomy [2,12,13,21].

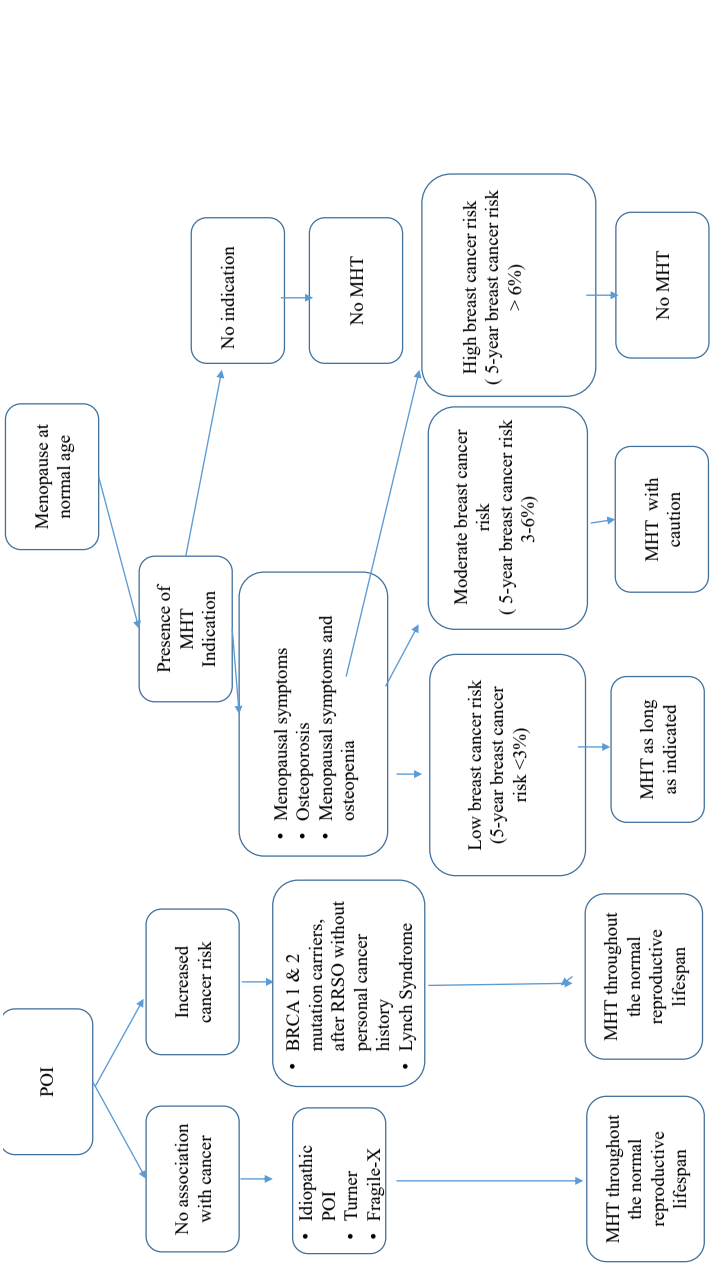


**Fig. 1.** Customization of menopause hormone therapy (MHT) use in premature ovarian insufficiency (POI) patients and in peri- and postmenopausal women in the context of breast cancer risk.

**Table 2**
Women with BRCA 1 & 2 mutations but without personal cancer history: Breast and ovarian cancer risks before and after RRSO and risk of using MHT.

| | BRCA1mutations | BRCA2 mutations |
|---|---|---|
| Breast cancer risk by age 80 | 72% | 69% |
| Ovarian cancer risk by age 80 | 44% | 17% |
| Age at which RRSO is recommended | 35 to 40, (upon completion of childbearing) | 40-45, (upon completion of childbearing) |
| Type of breast cancers | Often Triple-negative | Often oestrogen and progesterone receptor expressed |
| Main consequences of risk reduction following RRSO | Severely increased CVD risk (6 extra cases/1000 women-year) (71)<br>Increased osteoporosis risk<br>Menopause symptoms at an early age | Increased CVD risk<br>Increased osteoporosis risk<br>Menopause symptoms at an early age |
| Risk reduction following RRSO combined with E-PT [21,26] | EPT: HR 1.31 (95% CI 0.66−2.57, p = 0.44) | |
| Risk reduction following RRSO + TAH[a] | | |
| Risk reduction following RRSO combined with E-T [21,26] | ET: HR 0.73 (95% CI 0.41−1.32, p = 0.30) | |
| ISDO[b] | Unknown | Unknown |

RRSO: Risk-reducing salpingo-ophorectomy, TAH: Total abdominal hysterectomy, ISDO: interval salpingectomy with delayed oophorectomy. ET: Oestrogen-therapy, EPT: Oestrogen-progestin therapy. HR: Hazard Ratio. CVD: Cardiovascular.

[a] TAH may reduce small increased serous uterine cancer risk, and Tamoxifen endometrial cancer risk in BRCA1 carriers [21] permiiting ET rather than EPT supplementation.

[b] ISDO: no need for ET or EPT.

Armstrong et al. using a Markov model, estimated that RRSO lengthened life expectancy in BRCA1/2 mutation carriers, irrespective of whether MHT was used after surgery until the age of 50 [29]. In summary, BRCA1 and 2 patients have increased breast cancer risk. This risk may be reduced by RRSO. MHT is a treatment option for these women, if they have no personal cancer history yet. ET may be given to hysterectomized women, while EPT may be administrated to women who have undergone RRSO [2,3,10,29] (Tables 1 and 2) (Fig. 1).

*Women with lynch syndrome*

Lynch syndrome, formerly known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominantly inherited disorder of cancer susceptibility caused by germline mutations in the DNA mismatch repair (MMR) genes, MLH1, MSH2, MSH6, and PMS2 [30]. These patients have an increased colon, rectum, endometrium, stomach, ovary, ureter, renal pelvis, brain, small bowel, and hepatobiliary tract cancer risk at a young age, but an association with an increased breast cancer risk has been inconsistent [30]. Identified Lynch syndrome patients will have a prophylactic RRSO and Total Abdominal Hysterectomy (TAH). Although there are no data about the effect of MHT, it seems reasonable to commence MHT in these women.

## Breast cancer risk in peri- and postmenopausal women and MHT

*Breast cancer risk evaluation in peri- and postmenopausal women*

Breast cancer risk can be expressed various ways: Relative risks with 95% confidence intervals (RR: 95 % CI) have the advantage of hierarchising risks. Relative risks that are associated with a higher than four-fold risk, may be considered as important. These include: BRCA mutation carriers, a strong family history (several first-degree breast cancer relatives or relatives affected at young age) without evidence of a mutation, previous history of atypical hyperplasia, Lobular Carcinoma In Situ (LCIS), Ductal Carcinoma In Situ (DCIS), thoracic radiotherapy especially at a young age and increased breast density (BIRADS 4) (using the American College of Radiology (ACR) BIRADS classification, where BIRADS 1 is the lowest breast density and 4 the highest) [31]. Intermediate risk factors (i.e., a RR around 2 or less), include a family history at older age, obesity, diabetes, BIRADS 3- breast density, and reproductive factors such as a menarche at a young age, a first full-time pregnancy (FFTP) beyond the age of 35 years,

nulliparity, sedentarily and daily alcohol consumption of more than 3 glasses a day [31]. Protective factors include first full-time pregnancy before the age of 20, multiparity of more than 5 children, breast feeding for more than one year, BIRADS I-breast density, low Body Mass Index, low Bone Mineral Density, regular long and strenuous exercise [31].

Relative risks should be avoided when estimating risk for patient's guidance, because they do not take into consideration the prevalence and they are often misleading and not well understood by patients [32]. Alternatively, risk can be estimated using the 5-, 10- or lifetime risk of a patient to develop breast cancer in the presence or absence of risk factors [36]. Several calculators have been developed: The modified Gail- (https://bcrisktool.cancer.gov/), BOADICEA- (https://ccge.medschl.cam.ac.uk/boadicea/), BRACAPRO-(https://projects.iq.harvard.edu/bayesmendel/brcapro) and the CLAUS-model. The latter are mostly used to assess genetic risk. The IBIS II, also called Tyrer-Cuzick model (https://ems-trials.org/riskevaluator/) is easy to use and can be assessed to calculate the 5-year patient's risk in comparison to the general population of similar age. This is particularly useful for complex cases who accumulate several risk factors, although these models do not express the real individual risk, they are proxies and have limitations.

Finally, one can use absolute risk and attributable risk estimation which is the preferred way to explain a risk associated with a risk factor to patients [32].

*MHT and breast cancer risk*

Many studies reported that long term MHT administration is associated with some excess in breast cancer risk [1]. Still, high discrepancies exist between studies, which may result from differences in studied populations, designs and MHT regimens. It is beyond the scope of this article to discuss these in detail. Briefly, oestrogen only treatment was associated with a protective effect (in the WHI trials), but not in many observational trials, where a RR in the range of 1.1–1.3 has often been reported [33,38]. Oestrogen-progestin regimens are generally associated with a higher risk with a RR in the range of 1.5–2 [33,34]. Nevertheless, not all oestrogen-progestogen regimens entail the same risk. Medroxyprogesterone acetate, levonorgestrel and norethisterone acetate are associated with higher risk (RR in the range of 1.5–2) than micronized progesterone or dydrogesterone (RR in the range of 1.1–1.3) [34]. Discordant results were also reported concerning the use of tibolone: Breast cancer risk was reduced in the randomised placebo-controlled LIFT-trial, using half the conventional dose (1.25 mg) of tibolone in elderly osteoporotic women (Relative Hazard 0.32), while some observational studies reported no increase or an increase in breast cancer risk (RR 1.9) [35,36]. The tissue selective oestrogen complex, combining conjugated equine estrogens (CEE) with the SERM bazedoxifene (BZA), is available in some countries and constitutes an interesting alternative but needs to be studied further (47).

The latest analyses of the two randomised Women Health Initiative trials (WHI) trials are rather reassuring [33,38]. The attributable risk of a combined oestrogen-progestin regimen prescribed for 5 years to 1000 women, aged between 50 and 60 years, resulted in an excess of three cases/5000 women-year, while an oestrogen only regimen resulted in a reduced risk (2.5 less cases/5000 women-year) [38]. The latest WHI publications confirmed these results, but also reported, after a 20-year median cumulative follow-up, lower breast cancer mortality associated with oestrogen only therapy, and no excess in breast cancer mortality in oestrogen-progestin treated women [33].

*MHT customization in the context of breast cancer risk*

Most current guidelines consider that MHT is a safe treatment for women with menopausal symptoms and/or risk factors for osteoporosis, without contraindications to MHT, who are within 10 years of menopause or younger than age 60 years [1,37–42].

The decision to initiate or continue MHT should always be balanced, considering the indications for treatment, such as the presence of vasomotor symptoms, osteoporosis or osteopenia and cardiovascular prevention (especially in women with POI) [1,38–41]. Many authors suggest that a 5-year baseline breast cancer risk lower than 3% entails a low risk of prescribing MHT [32]. Most perimenopausal or recently postmenopausal women in need of MHT will fall in this category. For instance, using the IBIS calculator, the 5-year breast cancer risk would be 1.3% for a 52-year postmenopausal

woman without any personal history of breast cancer (https://ems-trials.org/riskevaluator/). A risk between 3% and 6% is considered as an intermediate risk, warranting caution, but this risk is acceptable when an indication for MHT is present. A 52-year-old woman, with a BIRADS 4-breast density or with a mother who developed a breast cancer at age 60, would have 5-year-breast cancer risk of 2% (https://ems-trials.org/riskevaluator/). Adding both risk factors will increase her risk at 4% (https://ems-trials.org/riskevaluator/). When the risk is higher than 6%, MHT is not indicated [32]. This is the case for a woman with a previous atypical hyperplasia of the breast (risk estimation 5.7%) or LCIS (12%) (https://ems-trials.org/riskevaluator/).

## Conclusion

We present an algorithm in Fig. 1 which summarises a practical guide on breast cancer risk in POI patients and in per- and postmenopausal women. For women with POI, many decisions are still based on low levels of evidence as assessed in Table 1. This underlines the importance of registries of menopause management in POI patients, as randomised trials are seldom feasible in these women. For most symptomatic or osteoporotic peri- and postmenopausal women, who have no contraindication to MHT, and are within 10 years of menopause or less than 60 years of age, MHT is a safe option, warranting an acceptable attributable breast cancer risk. Hysterectomized women should be prescribed oestrogen-only therapy, while women with an intact uterus should use combined oestrogen-progestogen therapy, favouring progestogens that have the lowest risk, such as micronized progesterone and dydrogesterone.

## Declaration of competing interest

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**Research agenda**

- There is a need of POI registries.
- Observational studies should include cardiovascular-, fractures, and cancers events.
- There is a need of RCT in POI patients.
- Need for evaluation of cardiovascular effects using surrogate outcomes (e.g. coronary artery calcium (CAC) score with computed tomography (CT)).
- Evaluation of cognitive benefits and risks of various regimens.

**Practice points**

- Investigate the aetiology of POI.
- Evaluate and correct baseline risk factors.
- Treat most POI patients, with MHT until at least the age of 50 years.

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