BMS, IMS, EMAS, RCOG and AMS Joint Statement on menopausal hormone therapy (MHT) and breast cancer risk in response to EMA Pharmacovigilance Risk Assessment Committee recommendations in May 2020

The British Menopause Society (BMS), International Menopause Society (IMS), European Menopause and Andropause Society (EMAS), Royal College of Obstetricians and Gynaecologists (RCOG) and Australasian Menopause Society (AMS) wish to clarify the evidence on the risk of breast cancer with menopausal hormone therapy (MHT) in response to the recommendations of the European Medicines Agency (EMA) - the central European drug regulatory body - Pharmacovigilance Risk Assessment Committee on 11-14 May 2020 that followed on from a meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) published in the Lancet on 30 August 2019.

The EMA Pharmacovigilance Risk Assessment Committee has mandated a safety update, specifically regarding breast cancer risk, to the Summary of Product Characteristics (SmPC) of all estrogen-containing MHT products. The update recommended emphasizing the increased risk of breast cancer with both estrogen-only and estrogen and progestogen containing MHT. This recommendation appears to follow on from the CGHFBC meta-analysis and does not appear to take into consideration the findings from the Women's Health Initiative (WHI) randomized trials findings nor their recent long-term follow up data.

The aim of this Position Statement is to make recommendations on best practice in the care of women with menopausal symptoms in response to the EMA Pharmacovigilance Risk Assessment Committee recommendations in May 2020.

We recognize that the menopause transition can have a significant impact on many women, with more than 75% experiencing menopausal symptoms, a quarter describing severe symptoms which may last as much as seven years or more, and a third experiencing long-term symptoms. MHT, compared with placebo, has been consistently shown to improve menopausal symptoms and it remains the most effective treatment that is also associated with significant improvement in overall quality of life.

We strongly believe that the findings from the CGHFBC meta-analysis should be considered in the context of the overall benefits obtained from using MHT, as referred to in this Position Statement.

Key messages from the BMS, IMS, EMAS, RCOG and AMS Position Statement

The BMS, IMS, EMAS, RCOG and AMS remain of the view that the CGHFBC meta-analysis provides important additional information on the risk of breast cancer with MHT. However, we strongly feel that this should not be interpreted in isolation and needs to be considered in the context of the overall benefits and risks associated with MHT intake to help women make an informed choice.

We believe that no arbitrary limits should be placed on the dose or duration of usage of MHT. This decision should be made on an individualized basis and should be considered in the context of the overall benefits obtained from using MHT, including symptom management and improved quality of life and the cardiovascular and bone protective effects associated with MHT.

The key points which the BMS, IMS, EMAS, RCOG and AMS wish to make in this Position Statement are summarized in the Table below:

Menopausal symptoms	The menopause transition can have a significant impact on many women, with more than 75% experiencing menopausal symptoms, a quarter describing severe symptoms, and a third experiencing long-term symptoms.
Treatments	MHT, compared with placebo, has been consistently shown to improve menopausal symptoms and overall quality of life and remains the most effective treatment for menopausal symptoms. For some women, MHT may not be suitable, and alternative treatments are available.
MHT and breast cancer risk – the CGHFBC meta-analysis	Results from the CGHFBC meta-analysis show a small increase in the absolute risk of breast cancer: **5-years intake of MHT starting at the age of 50 years and risk of breast cancer at age 50-69 years** ***For continuous combined MHT*** Increase from a baseline risk of 3/50 women not on MHT to 4/50 (i.e., 1 extra case in 50 women). ***For sequential combined MHT*** Increase from a baseline risk of 4/70 women to 5/70 (i.e., 1 extra case in 70 women).

	For estrogen only MHT Increase from a baseline risk of 13/200 women to 14/200 (i.e., 1 extra case in 200 women). **10-year intake of MHT starting at the age of 50 years and risk of breast cancer risk at age 50-69 years** ***For continuous combined MHT*** Increase from a baseline risk of 3/50 women not on MHT to 5/50 (i.e., 2 extra cases in 50 women). ***For sequential combined MHT*** Increase from a baseline risk of 4/70 women to 6/70 (i.e., 2 extra cases in 70 women). ***For estrogen-only MHT*** Increase from a baseline risk of 13/200 women to 15/200 (i.e., 2 extra cases in 200 women).
Interpretation of the evidence on the risk of breast cancer with MHT	The findings from the CGHFBC meta-analysis are in keeping with the NICE guidance 2015 analysis of the observational data on the risk of breast cancer and MHT. The findings from the CGHFBC meta-analysis should be explained to women when discussing the benefits and risks of MHT. However, discussions on the risk of breast cancer with MHT should also include the findings from the WHI placebo-controlled randomized trials and the large E3N observational studies, which reported on the risk of breast cancer risk in users of micronized progesterone compared with other progestogens. Neither of the latter two studies was included in the CGHFBC meta-analysis. The recently published WHI data showed a significant decrease in the risk of diagnosis of breast cancer with estrogen-only MHT and a significant reduction in breast cancer mortality compared with placebo. Women who took combined estrogen and progestogen MHT had an increased risk of breast cancer compared to placebo, in keeping with NICE guidance conclusions, but showed no significant difference in breast cancer mortality compared with placebo.

	The E3N observational studies suggested a lower breast cancer risk in users of micronized progesterone compared to users of more androgenic progestogens. Recommendations on the risk of breast cancer with MHT should take into consideration the findings from the WHI randomized trials and the observational data on micronized progesterone from the E3N study and those from the CGHFBC meta-analysis.
Informed consent	The risk of breast cancer should be considered in the context of the overall benefits and risks associated with MHT intake including menopausal symptom control, improved quality of life and the long-term impact on bone and cardiovascular health. The decision whether to take MHT, the dose of MHT and the duration of its use should be made on an individualized basis after discussing the benefits and risks with women to help them make an informed choice about their health and care.

MHT benefits and risks

Quality of life

Key points summary

- Menopausal symptoms affect 70-80% of all women.
- 25% of women describe their symptoms as severe.
- The average duration of menopausal symptoms is 7 years.
- 50% of women said their symptoms impacted their home life and 36% said the menopause impacted their social lives.

It is very relevant to consider the impact of menopause on women's quality of life and the beneficial effect that MHT has. Menopausal symptoms affect 70-80% of all women and these are described as severe by 25%. The average duration of menopausal symptoms has been reported to be 7 years, with up to a third of women reported experiencing symptoms beyond that. A national survey by the British Menopause Society in 2016 showed that women reported on average 7 menopause-related symptoms, with 79% experiencing vasomotor symptoms, 22% experiencing unexpected sleeping

problems / insomnia, 20% experiencing difficulty with memory / concentration and 18% experiencing unexpected joint aches. 42% of women indicated that the symptoms were worse or much worse than expected. 50% of women said their symptoms had impacted their home life and 36% said the menopause impacted their social life.

MHT and breast cancer risk - The CGHFBC meta-analysis

Key points summary

- Duration-dependent increase in the risk of breast cancer diagnosis with both unopposed estrogen and combined MHT.
- The risk is higher with continuous combined MHT regimens compared to cyclical.
- The risk of breast cancer remains elevated more than 10 years after discontinuing MHT.
- No estrogen dosage effect on the risk of breast cancer with MHT.
- Vaginal estrogen exposure did not increase the risk of breast cancer diagnosis.
- Only a small number of women on micronized progesterone were included. Therefore, conclusions regarding its impact on the risk of breast cancer diagnosis could not be determined from this meta-analysis.

The meta-analysis included 24 prospective observational studies with the median year of diagnosis of breast cancer in cases included in the review was 1999 for the North American and 2007 for the European studies.

The meta-analysis noted a duration-dependent increase in the risk of breast cancer diagnosis with both unopposed estrogen and combined MHT, the risk with the latter being greater. The review concluded that the risk is higher with continuous combined MHT regimens compared with cyclical and the risk of breast cancer remains elevated more than 10 years after discontinuing MHT. A modifying effect was noted for obesity.

The meta-analysis showed no estrogen dosage effect on the risk of breast cancer diagnosis with MHT and that vaginal estrogen exposure did not increase the risk of breast cancer diagnosis.

The increase in the risk of breast cancer diagnosis, as reported in the Lancet meta-analysis, is shown in the Table on pages 3-4. This report includes the absolute numbers for women aged 50-69 taking MHT for both 5 years and 10 years.

The overall findings from the CGHFBC meta-analysis are not new and are in keeping with the NICE menopause guideline 2015 recommendations. The review of the observational data by NICE showed similar findings to those reported in the CGHFBC meta-analysis. However, the conclusions in the NICE guideline came from the combined review of observational and RCT evidence. The WHI RCT data were not included in the CGHFBC meta-analysis and appears not to have been considered in the EMA Pharmacovigilance Risk Assessment Committee recommendations.

Further, there are a number of limitations in the methodology of the CGHFBC meta-analysis that need to be considered when interpreting the data. These include the following:

1. Some of the studies included in the CGHFBC meta-analysis had methodological limitations. A key example of this is that one of the main studies contributing to the meta-analysis, the Million Women Study, had a significantly increased risk of breast cancer at 4 months from commencement of recruitment (RR 1.19; 95% CI 1.09 to 1.30 for users of estrogen-only and RR 1.41; 95% CI 1.31 to 1.52 for users of combined MHT). It is highly unlikely that breast cancer would develop within 4 months from recruitment and this would, therefore, suggest that a significant proportion of women had undetected breast cancer at the time of entry into the study; this should be considered when interpreting the findings from the CGHFBC meta-analysis.
2. The CGHFBC meta-analysis only included a very small number of women on micronized progesterone and it appears that the large observational data from the French E3N study which suggested that micronized progesterone is likely to be associated with a lower risk of invasive breast cancer compared to that noted with other progestogens were not considered in the meta-analysis.
3. In addition, the CGHFBC meta-analysis did not report on breast cancer mortality. It would be relevant to note that long-term follow up of the WHI RCT up to 13 years showed no significant difference in breast cancer mortality or all-cause mortality with MHT compared with placebo. In addition, WHO and Eurostat data showed a decline in European breast cancer mortality over the last three decades in women of all ages. This steady decline pre-dated by over a decade, the sustained worldwide fall in MHT prescribing following publication of WHI and the Million Women Study in the early 2000s. The reduction is likely to be related to treatment improvements and

earlier diagnosis, including the impact of screening and is less likely to be related to the changing patterns in MHT use.

Following on from the CGHFBC meta-analysis, the Medicines and Healthcare products Regulatory Agency in the UK (MHRA) issued a Drug Safety Alert on the risk of breast cancer with MHT on 30 August 2019 that included the following recommendations:

''MHT should only be initiated for relief of postmenopausal symptoms that adversely affect the quality of life and should be continued only as long as the benefit in alleviating menopause symptoms outweighs the risks associated with MHT use.''

''MHT should be used at the lowest dose for the shortest amount of time''. The CGHFBC meta-analysis that this recommendation was based on showed no dosage effect with estrogen. It is, therefore, unclear what evidence the latter recommendation was based upon.

The EMA Pharmacovigilance Risk Assessment Committee recommendations mandated a safety update, specifically regarding breast cancer risk, to the Summary of Product Characteristics (SmPC) of all estrogen-containing MHT products. The update recommended emphasizing the increased risk of breast cancer with both estrogen-only and estrogen-progestogen containing MHT. This recommendation seems to follow on from the CGHFBC meta-analysis and does not appear to take into consideration the findings from the WHI randomized trials, including its recently published long-term follow-up outcomes.

The WHI long-term randomized clinical trials, published in JAMA 2020, reported on the association of MHT with breast cancer incidence and mortality and involved over 27,000 women, who were enrolled between 1993 to 1998 and followed-up through 2017. The report showed a significant decrease in the risk of breast cancer diagnosis (HR 0.78; 95% CI 0.65 to 0.93; P=0.005) and a significant reduction in breast cancer mortality (HR 0.60; 95% CI 0.37 to 0.97; P=0.04) when estrogen-only HRT is taken. Women who took combined estrogen and progestogen HRT had an increased risk of breast cancer compared to placebo (HR 1.28; 95% CI 1.13 to 1.45; P<0.001), in keeping with the NICE guideline conclusions, but had no significant difference in breast cancer mortality compared with placebo (HR 1.35; 95% CI 0.94 to 1.95; P=0.11). These important findings on breast cancer mortality contrast with the most recent follow-up data from the Million Women Study. Further, in contrast to the CGHFBC meta-analysis, the WHI study showed no significant increase in the risk of diagnosis of breast cancer

in women who were past users of HRT at the time of taking part in the WHI study compared to that in women who had not used HRT before taking part in the WHI study.

We believe that the findings from the CGHFBC meta-analysis should be explained to women when discussing the benefits and risks of MHT. However, discussions on the risk of breast cancer with MHT should also include the findings from the WHI placebo-controlled randomized trials and the large E3N observational studies, which reported on the risk of breast cancer risk in users of micronized progesterone compared with other progestogens. Neither of the latter two studies was included in the CGHFBC meta-analysis.

Osteoporosis

Key points summary

- Evidence from RCTs and meta-analysis shows that women using MHT have a significant reduction in the risk of any fracture compared with women not using MHT.

In addition to the potential cardiovascular benefits, MHT has been shown to have a significant protective effect against osteoporosis and related fragility fractures. The International Osteoporosis Foundation reports that a 50 years old woman has a 2.8% risk of death related to hip fracture during her remaining lifetime.

The NICE 2015 guideline on the diagnosis and management of the menopause assessed 20 RCTs that included sample sizes from 36 to 16,608 cases and 21 comparative cohort studies, which included sample sizes from 157 to 170,852 cases. The evidence from RCTs in women in current users of MHT showed a significant reduction in the risk of any fracture compared with women not using MHT. The evidence from comparative cohort studies showed a reduced risk of any and all fractures with current MHT use compared with non-use of MHT, whether previous or never use.

Further, a systematic review and meta-analysis by Zhu *et al.* 2015 included 28 studies with 33,426 participants and 2,516 fracture cases. Their meta-analysis noted a significant reduction in total fractures with MHT (RR 0.74; 95% CI 0.69 to 0.80), hip fractures (RR 0.72; 95% CI 0.53 to 0.98) and vertebral fractures (RR 0.63; 95% CI 0.44 to 0.91).

Cardiovascular disease (CVD)

Key points summary

- The timing MHT is initiated, referred to as the 'timing hypothesis' and 'the cardiovascular window of opportunity', can have a significant impact on the risk of CVD with MHT intake.
- Cochrane data-analysis shows that MHT initiated within 10 years of the menopause is likely to be associated with a reduction in coronary heart disease and cardiovascular mortality.
- Evidence from the Cochrane data-analysis and that from the long-term follow-up data of the WHI showed no increase in cardiovascular events, cardiovascular mortality or all-cause mortality in women who initiated MHT more than 10 years after the menopause.

Cardiovascular disease remains a leading cause of mortality in women worldwide. Given the potential cardiovascular beneficial effects reported with MHT initiated in women under the age of 60, as referred to above, this is a further aspect that should be considered as part of the benefits / risks assessment when counseling women about MHT.

There is compelling evidence that the timing MHT is initiated, often referred to as the 'timing hypothesis' and 'the cardiovascular window of opportunity', can have a significant impact on the risk of CVD with MHT intake.

The NICE 2015 guideline on the diagnosis and management of the menopause concluded in its literature review that starting MHT at the time of the menopause did not appear to be associated with an increase in the risk of cardiovascular disease.

Cochrane analysis by Boardman et al. 2015 demonstrated a significant reduction in cardiovascular events, cardiovascular mortality and all-cause mortality in women who commenced MHT within 10 years of onset of menopause compared to placebo.

Cochrane analysis findings that showed a reduction in all-cause mortality were from placebo controlled RCTs with a total number of 9,088 women. The analysis showed a significant reduction in all-cause mortality of 16/1000 with MHT compared with 22/1000 with placebo (RR 0.70, 95% CI 0.52 to 0.95). The Cochrane analysis also noted a significant reduction in coronary heart disease (including a reduction in cardiovascular mortality) from placebo-controlled RCTs, including 8,311 women. The analysis showed a significant reduction in coronary heart disease (death from cardiovascular causes

and nonfatal myocardial infarction) of 10/1000 with MHT compared with 18/1000 with placebo (RR 0.52; 95% CI 0.29 to 0.96).

For the group of women who commenced MHT more than 10 years after the menopause, both WHI long-term follow-up and Cochrane analysis showed no significant reduction, but relevant to mention, no significant increase in the risk of cardiovascular events, cardiovascular mortality or all-cause mortality in women who started MHT beyond the age of 60 years.

The Cochrane analysis was also supported by data from the Finnish nationwide reimbursement register and the Finnish national Cause of Death Register reported by Mikkola *et al.* (2015). In total, 489,105 women who used MHT (3.3 million MHT exposure years) were included. The rate of coronary heart disease-related deaths was reduced within the first year of MHT use compared to age-matched background population (IR 0.82; 95% CI 0.75 to 0.89) and this was positively related to MHT time exposure, with a risk reduction of 18-54% from 1 year to 10 years of use. The rate of stroke death (IR 0.82; 95% CI 0.74 to 0.92) and all-cause mortality (IR 0.88; 95% CI 0.85 to 0.91) was also reduced within the first year of MHT use. The risk reduction was positively related to MHT time exposure for stroke (18% to 39%) and all-cause mortality (12-38%) from 1 year to 10 years of use. These reductions were noted in both women receiving estrogen-alone and those receiving combined estrogen-progestogen preparations and were comparable for women who initiated MHT before the age of 60 years and those who started MHT after the age of 60 years. In absolute terms, women who used any regimen of MHT for 10 years or more had 19 fewer coronary heart disease-related deaths and 7 fewer stroke-related deaths per 1,000 women compared with controls.

Further, Salpeter et al. 2009 reported a meta-analysis that included pooled data from 19 randomized trials that included 16,000 women (mean age 55 years) followed up for 83,000 patient-years. The study showed a significant reduction in all-cause mortality with MHT intake compared with no treatment (RR 0.73; 95% CI 0.52 to 0.96). A similar conclusion was noted when data from 8 observational studies were added to the analysis (RR 0.72; 95%CI 0.62 to 0.82).

In addition, a recent long-term FU report from the WHI study by Manson et al. 2019 included a total sample size of 9,939 women aged 50-79 and of these 1,129 women were aged 50-59. The report showed a significant reduction in all-cause mortality HR 0.68, 95% CI 0.48 to 0.96 in women aged 50-59 who received estrogen therapy after bilateral salpingo-oophorectomy compared with those who

received placebo.

Risk of venous thromboembolism

Key points summary

- Compared with women not on MHT, the risk of venous thromboembolism is increased by oral intake MHT.
- Transdermal administration of estradiol is unlikely to increase the risk of venous thrombosis above that in non-users and is associated with a lower risk compared with oral administration of estradiol.

Compared with women not on MHT, the risk of venous thromboembolism is increased by oral intake MHT. However, there is no increased risk of venous thromboembolism associated with transdermal MHT compared with women not on MHT.

A meta-analysis by Scarabin (2018) reported on the risk of VTE with oral versus transdermal estrogen and progestogens and included 7 population-based observational studies (4 case-control and 3 cohort studies). A total of 26,471 VTE cases, of which 735 were users of transdermal estrogen and 3,103 users of oral estrogen, were included as well as 22,633 non-users. Women taking oral estrogen-only preparations had an increased risk of VTE compared to women not on MHT (RR 1.48; 95% CI 1.39 to 1.58). However, women taking transdermal estradiol preparations had no increased risk compared with women not taking MHT (RR 0.97; 95% CI 0.87 to 1.09).

In addition, evidence from large observational studies and case-controlled studies suggests that micronized progesterone and dydrogesterone are unlikely to increase the risk of venous thrombosis compared to other progestogens.

Conclusion

The BMS, IMS, EMAS, RCOG and AMS believe that any recommendations on the risk of breast cancer with MHT should take into consideration the collective evidence in this context including the CGHFBC meta-analysis and the findings from the WHI placebo-controlled randomized trials and the large E3N observational studies which reported on the risk of breast cancer risk in users of micronized progesterone compared with other progestogens.

We believe that no arbitrary limits should be placed on the dose or duration of usage of MHT. Further, we strongly feel that the risk of breast cancer with MHT should not be interpreted in isolation. This decision should be made on an individualized basis and considered in the context of the overall benefits obtained from using MHT, including symptom management and improved quality of life and the cardiovascular and bone protective effects associated with MHT.

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References

1. EMA Pharmacovigilance Risk Assessment Committee PRAC recommendations on signals Adopted at the 11-14 May 2020 PRAC meeting. https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-11-14-may-2020-prac-meeting_en.pdf
2. National Institute for Health and Care Excellence. Menopause: diagnosis and management. NICE, 2015.
3. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019;394:1159-68. doi: 10.1016/S0140-6736(19)31709-X 31474332.
4. Chlebowski RT, Anderson GL, Aragaki AK, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 2020;324(4):369–80. doi: 10.1001/jama.2020.9482.
5. Rossouw JE, Anderson GL, Prentice RL, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33. doi: 10.1001/jama.288.3.321 12117397.
6. de Villiers TJ, Hall JE, J. V. Pinkerton JV et al. Revised Global Consensus Statement on Menopausal Hormone Therapy, Climacteric 2016, doi: 10.1080/13697137.2016.1196047.
7. Baber RJ, Panay N, & the IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric 2016;19(2):109–50.
8. Marsden J, Pedder H, & Santen R. Risks and benefits of hormone replacement therapy before and after a breast cancer diagnosis. Post Reproductive Health 2020. doi: 10.1177/205336912093402610.
9. Hamoda H, Panay N, H Pedder et al. The British Menopause Society & Women's Health Concern 2020 recommendations on hormone replacement therapy in menopausal women. Post Reproductive Health (In Press).
10. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2018;25(11):1362–87. doi: 10.1097/GME.0000000000001241.
11. Fournier A, Mesrine S, Dossus L, et al. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. Breast Cancer Research and Treatment 2014;145(2):535–43.

12. Fournier, A., Berrino, F., & Clavel-Chapelon, F. Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort study. Breast Cancer Research and Treatment 2008;107(1):103–11.
13. Avis NE, Carolina N and Crawford SL. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA 2015;175:531–9.
14. The British Menopause Society. https://thebms.org.uk/wp content/uploads/2016/04/BMSNationalSurvey-MARCH2017.pdf.
15. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in postmenopausal women. Cochrane Database Syst Rev 2015;3:CD002229.
16. Manson JE, Aragaki AK, Rossouw JE, etal. WHI Investigators. Menopausal hormone therapy and long-term all-cause and cause-specific mortality. JAMA 2017;318:927–38. doi: 10.1001/jama.2017.11217 28898378.
17. Manson JE, Aragaki AK, Bassuk SS et al. WHI Investigators. Menopausal Estrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy: A Randomized Trial. Ann Intern Med. 2019. doi: 10.7326/M19-0274.
18. Mikkola TS, Tuomikoski P, Lyytinen H et al. Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. Menopause. 2015;22(9):976–83. doi: 10.1097/GME.0000000000000450.
19. Salpeter SR, Cheng J, Thabane L et al. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. Am J Med. 2009;122(11):1016–22.e1. doi: 10.1016/j.amjmed.2009.05.021.6.
20. Beral V, Reeves G, Bull D, Green J; Million Women Study Collaborators. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. J Natl Cancer Inst. 2011;103(4):296-305. doi: 10.1093/jnci/djq527.
21. Zhu L, Jiang X, Sun Y, Shu W. Eect of hormone therapy on the risk of bone fractures: a systematic review and meta-analysis of randomized controlled trials. Menopause. 2016;23(4):461–70. doi: 10.1097/GME.0000000000000519.