Could perimenopausal oestrogen prevent breast cancer?

[1]**Isaac Manyonda** BSc PhD MRCOG FICOG (Hon)
[2]**Vikram Talaulikar** MD MRCOG PhD
[3]**Roxanna Pirhadi** Pharm.D MPharm IP PG Dip
[4]**John Ward BSc (Hons)**
[5]**Dibyesh Banerjee** FRCS
[6]**Joseph Onwude** MBBS MSc DLSH&TM FRCOG

[1]Professor / Consultant in Obstetrics & Gynecology, Department of Obstetrics and Gynecology, St George´s University Hospitals NHS Foundation Trust / St George's, University of London, London, United Kingdom.

[2]Associate Specialist, Reproductive Medicine Unit, EGA Wing, University College London Hospital, 235 Euston Road, London NW1 2BU.

[3]Senior Lecturer, Faculty of Health, Education, Medicine and Social Care, Anglia Ruskin University, Second Floor William Harvey Building, Bishop Hall Lane, Chelmsford CM1 1SQ

[4]Medical Student, St George's, University of London, London, United Kingdom.

[5]Consultant in Breast Surgery, Department of Surgery, St George´s University Hospitals NHS Foundation Trust, London, United Kingdom.

[6]Consultant Gynaecologist, The Chelmsford Private Day Surgery Hospital, Fenton House, 85-89 New London Road, Chelmsford CM2 0PP.

All authors (IM, VST, RP, JW, DB, JO) report no conflict of interest.

Correspondence:

Professor Isaac T Manyonda
Department of Obstetrics and Gynaecology,
St George's University Hospitals NHS Foundation Trust &
St George's, University of London,
Blackshaw Road, Tooting,
London SW17 0QT United Kingdom
E-mail: imanyond@gmail.com, imanyond@sgul.ac.uk

Running title: Oestrogen therapy and breast cancer

Abstract

Breast cancer is the commonest cancer among women in the western world, accounting for up to 30% of all cancers in women. There is a long-standing controversy about the potential link to hormone replacement therapy (HRT), with large observational studies suggesting that HRT increases the risk, while the Women's Health Initiative (WHI), a prospective, randomised placebo-controlled trial has reported several times over a period of 20 years that combined (oestrogen and progestogen) HRT increases the risk, while oestrogen-only HRT given to women who have had a prior hysterectomy, is associated with a significantly reduced risk of developing breast cancer.

Key words: Menopause, HRT, Regimens,

Tweetable abstract:

Breast cancer is the commonest cancer among women in the western world. There is a long-standing controversy about the potential link to hormone replacement therapy (HRT), with large observational studies suggesting that HRT increases the risk, while the Women's Health Initiative, a prospective, randomised placebo-controlled trial has reported several times over a period of 20 years that combined (oestrogen and progestogen) increases the risk, while oestrogen-only HRT (ERT), given to women who have had a prior hysterectomy, is associated with significantly reduced risk of developing breast cancer, as well as significantly reduced mortality from the disease. We argue that it is not just semantics to suggest that the significant reduction in incidence of breast cancer, and reduction in mortality from the disease in women who took ERT versus those who took placebo robustly points to a protective/preventative effect of oestrogen.

The causation of breast cancer

Traditionally, it has been thought that oestrogens could play an important role in the pathophysiology of breast cancer, firstly because the female breast contains an abundance of oestrogen receptors, and secondly because of the observation that oestrogens can aggravate oestrogen receptor-positive breast cancer[1]. Neither are sustainable as possible explanations since firstly, breasts are only one of many organs that are suffused with oestrogen receptors (others include the brain, eyes, hair, nails, the skin, fatty tissues, muscles, cartilage, bones and blood vessels) and there is no concern about oestrogen-related cancer in these organs (although receptor density could explain differences). Secondly, not unexpectedly there have been women who have been diagnosed with breast cancer soon after commencing HRT. This of course does not prove causation, and in fact the mortality from breast cancer in these situations is actually often low[2], suggesting that the process of carcinogenesis had already started, and commencing oestrogens might have actually allowed an earlier diagnosis[3]. Thus despite being the commonest cancer in women in the developed western world, and notwithstanding the intense research activity aimed at it, the mechanism(s) by which breast cancer develops remains an enigma. There are of course a number of theories out there, including a role for endocrine disruptors[4], but these continue to be researched with no current resultant effective preventative or therapeutic interventions.

The epidemiology of breast cancer – impact of HRT versus life-style factors

In the UK, it is estimated that if 1000 otherwise healthy women who are not on HRT and aged 50-60 years are followed up over 5 years, 23 of them will develop breast cancer[5]. Figure 1 illustrates that if another 1000 such women who have an intact uterus are given cHRT, an additional 4 women (total 27) will develop breast cancer, while in a 1000 who have had a hysterectomy and therefore can be given oestrogen-only therapy (ERT), 4 fewer women (total 19) will develop the disease. Therefore, while cHRT is associated with an increased risk of breast cancer, ERT does not increase the risk, and if anything, appears to be associated with a reduced risk.

To further put the issue into perspective, the impact of life-style factors has been added (see **figure 1**). Amongst smokers, there will be an additional 3 cases of breast cancer (total 26), while 2 units of alcohol per day will add 5 women to the afflicted (total 28), and obesity (BMI >30) will add a phenomenal 24 women, giving a total of 47 in 1000. Conversely, exercise lasting 2.5 hours per week will reduce the number by 7 (total 16). These numbers illustrate that although cHRT increases the risk of breast cancer, the increase is relatively small compared to the risk posed by other modifiable risk factors, and that the risk is amenable to even simple interventions like exercise. If phrases such as “exercise prevents breast cancer” could be used to promote women’s health, could

the parallel phrase “oestrogen-only HRT prevents breast cancer” be acceptable? It is useful to consider what the research evidence shows.

HRT and breast cancer – evaluating the evidence from research

Over the years, issues relating to HRT and breast cancer have generated huge controversy, debates and divided opinions among the healthcare professionals as well as the general public, usually resulting in women who might otherwise benefit from HRT abandoning it or being denied it by their physicians. This has often been a result of the way in which research findings have been interpreted, and so it is worthwhile to briefly discuss how evidence is evaluated before a discussion of what the evidence actually says with regard to whether oestrogen could protect against breast cancer.

Retrospective observational studies are not useful to prove a “cause and effect relationship” because they start from the outcome (breast cancer) and can only measure the risk of exposure to oestrogens. They cannot successfully eliminate bias and confounding between exposure and disease. A **prospective cohort study** is the next level of evidence for the “cause and effect relationship” between intervention (oestrogen) and disease (breast cancer), but it has other requirements such as strength of association, biologic plausibility, biologic credibility among different studies[6]. Results from a **valid randomized placebo-controlled study** are traditionally regarded as the best evidence of causation between intervention and disease provided the comparison groups are similar at baseline. This requirement for comparability at baseline eliminates bias, and known and unknown confounders[7,8]. There is a paradigm with how significant results are interpreted. There are three scenarios:

Firstly, when the relative risk (RR) or hazard ratio (HR) is > 1.0 with 95% Confidence intervals that do not include 1.0, it declares a significant risk in the treatment group compared to the placebo group. Biologic plausibility is then sought to explain the causal relationship between treatment and disease, particularly if the quantum of the RR is large.

Secondly, when the relative risk (RR) or hazard ratio (HR) is > 1.0 with 95% Confidence intervals that include 1.0, this declares a non-significant risk in the treatment group compared to the placebo group. It is then stated that the intervention does not cause the disease.

Thirdly, when the relative risk (RR) or hazard ratio (HR) is < 1.0 with 95% Confidence intervals that do not include 1.0, this declares a significant reduced risk in the treatment group compared to the placebo group. If this is so, such a result is often interpreted as ‘no increase in risk’ but in fact the result means a significant reduction in risk and that the treatment prevents the disease. This is not just a matter of semantics, as will become clear in the current views of whether oestrogen could prevent breast cancer.

HRT and breast cancer: the evidence from observational studies

Probably the two most influential observational studies on breast cancer risk in association with HRT are the "Collaborative Re-analysis"[9] and the "Million Women"[10] studies. The Collaborative Re-analysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer[9] concluded that the risk of having breast cancer diagnosed is increased in women using HRT and increases with increasing duration of use. This effect is reduced after cessation of use of HRT and has largely, if not wholly, disappeared after about 5 years. The general implication was that HRT caused breast cancer. This re-analysis of observational studies included retrospective and prospective studies. Shapiro et al (2011)[11] tested the re-analysis on the basis of standard criteria when an observational study asserts causality. They examined the following factors: time order, bias, confounding, statistical stability, strength of association, dose-duration response, internal and external consistency and biologic plausibility. They concluded that the causality link reached by the Collaborative Re-analysis was defective. This independent report means that the Collaborative re-analysis has low scientific validity because of serious significant epidemiological faults.

The Million Women's Study[10] was a prospective cohort of UK women aged 50-64 years invited to undergo screening mammography at 3-yearly intervals. Among 828,923 postmenopausal women who were current users of HRT and followed for an average of 2.6 years, the study concluded that current use of HRT was associated with increased breast cancer incidence and mortality and the effect was substantially greater for oestrogen-progestogen combinations (cHRT) than for other types of HRT. Again, the general implication was that HRT caused breast cancer. This prospective study had many methodological shortcomings and the most cogent was that it did not exclude breast cancers that appeared within one year, as they were most likely to have been present at baseline. Shapiro et al (2011)[12] also tested the Million Women's Study on the basis of standard criteria when an observational study asserts causality. They examined the following factors: time order, bias, confounding, statistical stability, strength of association, dose-duration response, internal and external consistency and biologic plausibility. They concluded that HRT may or may not increase the risk of breast cancer, but the Million Women's Study did not establish that it does. The causality link was unreliable because of defects in quality of design, execution, analysis and interpretation. They commented that size alone did not guarantee that the findings are reliable. This independent report means that the Million Women's Study again has little scientific validity because of serious epidemiological faults. However, the Million Women's Study differentiated that there was a lower risk of incident breast cancer between women on ERT or Tibolone compared to women on cHRT[10].

HRT and breast cancer: the evidence from randomised controlled studies

The Women's Health Initiative (WHI) studies are without doubt the most influential of any of the prospective, placebo-controlled randomised trials of HRT and breast cancer risk. The research comprised two randomised trials that included 27,347 postmenopausal women, mean age 63.4 (SD 7.2) all of whom had a negative mammogram and no prior breast cancer at baseline. Enrolment took place from 1993 to 1998, with participants being contacted for follow-up every 6 months through 2005 and annually from then on, and mortality data being gathered from follow-up and the National Death Index. In the first trial, which included 16,608 women with a uterus, 8,506 women received 0.625 mg/day of conjugated equine oestrogen (CEE) plus 2.5mg/day of medroxyprogesterone acetate (MPA), while 8,102 received placebo. In the second trial, the women had had a hysterectomy and therefore did not need MPA: 10,739 women were randomized to 0.625 mg/day CEE (5,310 women) while 5,429 women received placebo. The first trial ended in 2002 after a median intervention period of 5.6 years, and the second trial ended in 2004 after a period of 7.2 years.

(i) Outcomes from cHRT versus Placebo

This WHI study reported six times. The first five reports between 2002 and 2009[13-18] were based on a randomised controlled trial. The fifth report incorporated a prospective observational cohort with follow-up for a further 8 years.[19]

The second report[14] focused more on women who developed breast cancer after an average of 5.6 years in the randomised controlled trial. Shapiro et al, (2011)[18] highlighted that there was a degree of contamination with 331 women in the concurrent oestrogen replacement trial who still had a uterus, who were unblinded and added to the combined oestrogen plus progesterone group versus placebo trial. Nevertheless, for all breast cancers, the hazard ratio was 1.24 [95% CI 1.02 to 1.50] when 8,507 women aged 50-79 years who received cHRT were compared to 8,102 similar women who received placebo.

Based on the WHI randomized controlled trial only and not the sixth report[14] which was a combination of randomised controlled trial and follow-on observational study, the WHI studies of cHRT versus placebo show a causal link between cHRT_and incidence of breast cancer. The long-term results confirm this causality[20].

(ii) Outcomes from ERT versus placebo

This WHI study reported five times. The first report was held to be valid because, apart from similar baseline characteristics, there were similar proportions of un-blinding, similar discontinuation rates, and similar proportions of those who were prescribed HRT by their own doctors. The second report focused more on women who developed breast cancer after an average of 7.1 years in the randomised controlled trial. In the 'intention to treat analysis', there was a 23% non-significant reduction in the risk of breast cancer compared to placebo (relative risk ratio: 0.77; 95% CI 0.59-1.01). However, in an 'as treated analysis' which satisfies time order, minimises detection bias and where confounding was unlikely, there was a 33% significant reduction in the risk of breast

cancer compared to placebo (RR: 0.67; 95% CI 0.47-0.97). These results persisted after 10.7 years.
Shapiro et al (2011)[19] stated that the evidence suggests that unopposed oestrogen does not increase the risk of breast cancer and may even reduce it. The latter possibility, however, was initially based on statistically borderline evidence. The long-term results confirm this lack of a causal link between unopposed oestrogen and incidence of breast cancer, and that unopposed oestrogens do not increase the risk of breast cancer, in fact reducing it[20].

What is unique and remarkable about the WHI studies of HRT and breast cancer risk is that once again, after a median of 20.3 years of follow-up, and with mortality data now available for more than 98% participants, outcomes have been reported / updated in JAMA in July 2020[21]. The key findings were as follows :

(i) CEE alone (ERT) was associated with fewer cases of breast cancer (238 cases, annualised rate 0.30%), compared with placebo (296 cases, annualised rate 0.37%; hazard ratio 0.78; 95% confidence interval, 0.65-0.93; P = .005).

Furthermore, CEE alone was also associated with lower mortality (30 deaths, annualised mortality rate 0.031%), compared with placebo (46 deaths, annualised mortality rate 0.046%; HR 0.60; 95% CI, 0.37-0.97; P = .04).

(ii) In contrast, CEE plus MPA (cHRT) was linked with more cases of breast cancer (584 cases, annualised rate 0.45%) than placebo (447 cases, annualised rate 0.36%; HR 1.28; 95% CI, 1.13-1.45; P < .001). In regard to mortality, there was no statistically significant difference between CEE plus MPA (71 deaths, annualised mortality rate 0.045%) and placebo (53 deaths, annualised mortality rate 0.035%; HR 1.35; 95% CI, 0.94-1.95; P = .11).

Thus, the WHI studies show that taking CEE alone for up to 7 years confers protection against breast cancer for at least 20 years, while taking the combination therapy CEE and MPA for just 5 years increases the risk, which persists for at least 20 years. Is it the combination therapy, or is it the progestogen alone, that causes the breast cancer? While the answer is not as clear cut as might be imagined, it should be remembered that **o**estrogens increase glandular tissue, while it is the progestogens that cause mitosis of breast tissue – cancer represents uncontrolled mitosis.

Implications of the new insights on the preventative benefits of oestrogen
The evidence now compels a paradigm shift from the traditional thinking that oestrogen could cause breast cancer to a recognition that it actually prevents the disease, and that when the disease does occur (no preventative intervention achieves a 100% preventative effect), it is often picked up early and mortality is reduced by up to 44%. Therefore, rather than being left to fear oestrogen, the majority of perimenopausal

women should be offered the hormone, on its own in those who have had a hysterectomy, and with a progestogen-releasing intrauterine device in those with an intact uterus. This cheap and safe hormone also has other preventative potential. Oestrogen prevents osteoporosis[22], a condition that can lead to bone fractures with a major impact on quality of life, increased mortality and is a significant drain on NHS resources[23]. In the premenopausal phase women enjoy protection against cardiovascular disease, but soon catch up with men after the menopause: oestrogen given as HRT protects against cardiovascular disease in women[24]. A gender difference in favour of women in terms of infection rates and mortality has been clearly observed in a variety of pandemic-prone viral infections including Covid-19[25], SARS[26] and MERS[27], and oestrogen has been implicated either by boosting the immune system, both innate and adaptive, and also by direct action on cell types such as the vascular endothelium[28,29]. Oestrogen reduces the risk of colorectal cancer[30], and there is increasing evidence from in-vitro, animal and human experimentation that it may protect against dementia[31]. Finally, oestrogen is the most effective intervention in the treatment of menopausal symptoms[32,33] such as hot flushes and night sweats, vaginal dryness, shedding hair and dry skin, emotional lability to name but a few of the symptoms women may suffer in the menopausal transition. At a time when there is an emphasis on prevention as a major strategic approach to improve the nation's health[34], oestrogen should be recognized for its huge potential.

Concluding remarks

It is generally accepted that contemporary best clinical practice should be evidence-based, with the best clinical evidence coming from randomised clinical trials. The WHI study of ERT versus placebo in women with a prior hysterectomy is a most robust piece of research – prospective, randomized, placebo-controlled and with a 20 year follow up – which now compels a direct interpretation of its finding, namely that exposure to exogenous oestrogen (ERT) prevents breast cancer. This is of profound importance, not only in relation to the prevention of the most common cancer in women in the western world, but also because oestrogen, whilst being cost-effective and well-tolerated also has other preventative properties against osteoporosis and cardiovascular disease, to name but two. If the medical profession are struggling with the required paradigm shift in their attitude to ERT, then a well-designed, adequately powered, prospective randomised trial with so many spin-offs is eminently doable. Results could be available in less than ten years, and if such results support those from the WHI, then there would be no further arguments or debate.

Disclosure of interests: None of the authors have any conflicts of interests to declare

Contribution to authorship: JO and IM wrote the first draft of the manuscript. JO, IM, RP, VT, DB and JW contributed to analysis of the studies and writing of the final draft of the manuscript.
Details of ethics approval: Not applicable.
Funding: No funding was received for preparation of this manuscript.

References

1. Yue W, Wang JP, Li Y, et al. Effects of estrogen on breast cancer development: Role of estrogen receptor independent mechanisms. *Int J Cancer*. 2010;127(8):1748-1757. doi:10.1002/ijc.25207.
2. Mikkola TS, Savolainen-Peltonen H, Tuomikoski P, Hoti F, Vattulainen P, Gissler M, Ylikorkala O. Reduced risk of breast cancer mortality in women using postmenopausal hormone therapy: a Finnish nationwide comparative study. Menopause. 2016 Nov;23(11):1199-1203. doi: 10.1097/GME.0000000000000698. PMID: 27465718.
3. Onwude JL. Response to Hormone Replacement Therapy and the breast, BMJ 2002; 323: 1381.
4. Macon MB, Fenton SE. Endocrine disruptors and the breast: early life effects and later life disease. *J Mammary Gland Biol Neoplasia*. 2013;18(1):43-61. doi:10.1007/s10911-013-9275-7.
5. Women's Health Concern. Factsheet: Understanding the risks of breast cancer. A comparison of lifestyle risk factors versus Hormone Replacement Therapy (HRT) treatment. March; 2017, Buckinghamshire, UK. https://thebms.org.uk/wp-content/uploads/2016/04/WHC-UnderstandingRisksofBreastCancer-MARCH2017.pdf.
6. Onwude JL, Response to Short term use of HRT increases risk of ovarian cancer, analysis finds. BMJ 2015; 350: h840.
7. Chlebowski RT, Hendrix SL, Langer RD et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003; 289: 3243–3253.
8. Anderson GL, Chlebowski RT, Aragaki AK et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncology 2012; 13: 476–86.
9. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet. 1997; 350:1047-59.

10. Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. Lancet 2003; 362: 419-427.
11. Shapiro S, Farmer RDT, Seaman H et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies Part 1. The Collaborative Reanalysis. J Fam Plann Reprod Health Care 2011; 37: 103-109.
12. Shapiro S, Farmer RDT, Stevenson JC et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 4: the Million Women Study. J Fam Plann Reprod Health Care. 2012; 38(2): 102-9.
13. 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;288:321–333.
14. Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. Maturitas 2006;55:103–115.
15. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 2008;299:1036–1045.
16. Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. Am J Epidemiol 2008;167:1207–1216.
17. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 2009;360:573–587.
18. Shapiro S, Farmer RD, Mueck AO et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies: part 2. The Women's Health Initiative: estrogen plus progestogen. Fam Plann Reprod Health Care 2011; 37: 165 -172.
19. Shapiro S, Farmer RD, Mueck AO et al. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies: part 3. The Women's Health Initiative: Unopposed estrogen. J Fam Plann Reprod Health Care. 2011; 37(4): 225-30.
20. Chlebowski RT, Garnet L Anderson GL, Aragaki AK et al. Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The Women's Health Initiative Randomized Trials. San Antonio Breast Cancer Symposium, December 13, 2019.
21. 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):369–380. doi:10.1001/jama.2020.9482.
22. Gambacciani M, Levancini M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. *Prz Menopauzalny*. 2014;13(4):213-220. doi:10.5114/pm.2014.44996.
23. Leal J, Gray AM, Prieto-Alhambra D, et al. Impact of hip fracture on hospital care costs: a population-based study. Osteoporos Int. 2016;27(2):549-558. doi:10.1007/s00198-015-3277-9.

24. Lobo RA, Pickar JH, Stevenson JC, Mack WJ, Hodis HN. Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. Atherosclerosis 2016;254:282-90 http://www.ncbi.nlm.nih.gov/pubmed/27745704.
25. Jin JM, Bai P, He W, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health. 2020;8:152.
26. La Vignera S, Cannarella R, Condorelli RA, Torre F, Aversa A, Calogero AE. Sex-Specific SARS-CoV-2 Mortality: Among Hormone-Modulated ACE2 Expression, Risk of Venous Thromboembolism and Hypovitaminosis D. Int J Mol Sci. 2020;21(8).
27. Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. Lancet Infect Dis. 2018;18(8):e217-e227.
28. Manyonda IT, Pereira RS, Makinde V, Brincatb M, Varrna RT. Effect of 17P-oestradiol on lymphocyte subpopulations, delayed cutaneous hypersensitivity responses and mixed lymphocyte reactions in post-menopausal women. Maturitas. 1992;14:201-10.
29. Pirhadi R, Sinai Talaulikar V, Onwude J, Manyonda I. Could Estrogen Protect Women From COVID-19?. Journal of Clinical Medicine Research, North America, 12, sep. 2020. Available at: <https://www.jocmr.org/index.php/JOCMR/article/view/4303/25893250.
30. Johnson JR, Lacey JV Jr, Lazovich D, et al. Menopausal hormone therapy and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2009;18(1):196-203. doi:10.1158/1055-9965.EPI-08-0596.
31. Simpkins JW, Perez E, Wang X, Yang S, Wen Y, Singh M. The potential for estrogens in preventing Alzheimer's disease and vascular dementia. Ther Adv Neurol Disord. 2009;2(1):31-49. doi:10.1177/1756285608100427.
32. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev. 2004;2004(4):CD002978. Published 2004 Oct 18. doi:10.1002/14651858.CD002978.pub2.
33. Fait T. Menopause hormone therapy: latest developments and clinical practice. Drugs Context. 2019;8:212551. Published 2019 Jan 2. doi:10.7573/dic.212551.
34. Public Health England. PHE Strategy 2020-25. Protectine and improving the nation’s health. September 2019, London, UK.