Supplementary Methods

We considered four hypothetical consultands (unaffected women) with different breast cancer family history profiles, modelling their future breast cancer risk from age 50 to age 80 years old. For this we used the validated BOADICEA V.6 breast cancer prediction model, as implemented in the CanRisk tool (www.canrisk.org), assuming the UK age-specific and calendar period-specific population incidences for invasive breast cancer[1,2]. BOADICEA employs complex segregation analysis to model the familial risks of breast cancer, incorporating both established breast cancer susceptibility genes and a residual familial polygenic component. It can accommodate any cancer family history scenario, taking into account the exact ages at cancer diagnosis and ages for unaffected relatives. BOADICEA also considers lifestyle/hormonal cancer risk factors including MHT use, applying a distribution of MHT usage of 0.913 (never/past), 0.011 (current oestrogen-only) and 0.076 (current other type), based on data from Health Survey data in England in 2005 and 2006[3–5]. For the purpose of these calculations, we first determined the estimated risk for the hypothetical consultands assuming no prior use of MHT. We then combined these predicted breast cancer risks with the proposed MHT exposure to calculate a personalised breast cancer risk.

Relative risk estimates for the association of MHT usage with breast cancer risk were obtained from the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) 2019 meta-analysis of 24 prospective studies of MHT usage involving 108,647 cases of female breast cancer[6]. We considered four types of MHT as defined in the CGHFBC study: combined (all), combined-intermittent (combined-cyclical), combined-daily (combined-continuous) and oestrogen-only. For each, we considered three durations of MHT administration: ages 50.0 to 51.0 (one year), ages 50.0 to 55.0 (five years) and ages 50.0 to 60.0 (ten years), using relative risks for "current" and "past" usage as estimated within the CGHFBC study (Supplementary Table 1). The relative risks for combined-intermittent and combined-daily MHT were calculated as one sixth lower and one sixth higher than those for combined-all MHT, as per findings from CGHFBC analysis[6]. The increased risk of breast cancer beyond MHT cessation was assumed to discontinue at age 70, as per the CGHFBC findings. To calculate the risk of breast cancer by MHT use we assumed the following model for breast cancer incidence:

$$h(t) = h_0(t)\exp\left(\beta(t) \times X\right)$$

where $h_0(t)$ is the predicted breast cancer incidence at age *t* by BOADICEA assuming no MHT use, under the family history assumptions (as above); $\exp\left(\beta(t)\right)$ is the applicable RR estimate for MHT use at age *t* based on the CGHFBC estimates (assumed to be 1 from age 70 onwards); and *X* is an indicator variable taking value 0 if there was no MHT use, and 1 if the consultand used MHT. The cumulative risk of developing breast cancer between ages 50 and age 50+*x*, in absence of mortality was then calculated using standard survival analysis theory as:

$$\int_0^x h(50+s)\exp\left(-\int_0^s h(50+u)du\right)ds$$

The cumulative risks of breast cancer were calculated from age 50 up to ages 55, 60, 65, 70 and 80. To calculate the risk of breast cancer associated with MHT use, the risk difference was calculated by subtracting the cumulative risk for a consultand with specified MHT usage from a consultand with the same family history profile but no MHT usage.

We used 10-year net breast-cancer specific mortality rates from 2008-2017, stratified by 10-year age-band, provided by NDRS (National Disease Registration Service, NHS England (formerly Public Health England))[7]. Net mortality estimates are calculated by comparing the survival of cancer patients with that expected based on the general population of the same profile of age, sex and socio-

economic status[8]. These mortality rates were considered separately for diagnoses of (i) all invasive breast cancers, and (ii) ER-positive invasive breast cancers only. To calculate the baseline breast cancer-specific mortality ascribed to their family history, we applied the 10-year net (breast-cancer-specific) mortality rate for all breast cancers to the per-decade baseline cumulative breast cancer risk (no MHT) for each consultand profile. For additional breast cancer-specific mortality consequent from MHT exposure for each consultand profile, we applied the 10-year breast cancer-specific mortality rate for ER-positive breast cancers to the per-decade MHT-related cumulative breast cancer risk, under the assumption that MHT confers risk of ER-positive breast cancer[9]. We summed the breast cancer-specific baseline mortality with the MHT-related mortality for each decade 50.0-60.0 (from turning 50 years to turning 60 years), 60.0-70.0 and 70.0-80.0 and then in total for breast cancers diagnosed during the age window of 50.0-80.0 (hereafter presented as simple integer ages). A summary of assumptions made in the modelling is presented in Supplementary Table 2.

Supplementary Table S1: Relative risks of breast cancer associated with type and duration of use of menopausal hormone therapy. Derived from relative risks of breast cancer calculated from collaborative analysis of 24 prospective studies of MHT usage involving 108,647 cases of female breast cancer, for “current usage” and for “past usage” through to age 70, for windows of MHT exposure of <1 year (for 1 year MHT 50.0 to 51.0), 1-4 years (for 5 years MHT 50.01-55.0) and 5-9 years (for 10 years MHT 50.01-60.0).

	Years of use of MHT (from 50)	**Y0-1**	**Y1-5**	**Y6-10**	**Y11-15**	**Y16-20**
	Age	**50.0-51.0**	**50.0-55.0**	**55.0-60.0**	**60.0-65.0**	**65.0-70.0**
Combined - all types	1 year 50.0 to 51.0	1.31	1.06	1.06	1.06	1.06
	5 years 50.01-55.0	1.60	1.60	1.18	1.18	1.18
	10 years 50.01-60.0	1.60	1.60	1.96	1.36	1.36
Combined – daily (continuous)	1 year 50.0 to 51.0	1.36	1.07	1.07	1.07	1.07
	5 years 50.01-55.0	1.70	1.70	1.21	1.21	1.21
	10 years 50.01-60.0	1.70	1.70	2.12	1.42	1.42
Combined – intermittent (cyclical)	1 year 50.0 to 51.0	1.26	1.05	1.05	1.05	1.05
	5 years 50.01-55.0	1.50	1.50	1.15	1.15	1.15
	10 years 50.01-60.0	1.50	1.50	1.80	1.30	1.30
Oestrogen-only	1 year 50.0 to 51.0	1.27	1.14	1.14	1.14	1.14
	5 years 50.01-55.0	1.28	1.28	1.08	1.08	1.08
	10 years 50.01-60.0	1.28	1.28	1.21	1.13	1.13

Supplementary Table S2. Assumptions applied in risk modelling

Assumption and implication	Reference
The consultand is peri-menopausal at time of proposed administration of MHT (ie not more than 1 year post discontinuation of menses). If MHT were initiated significantly after discontinuation of menses, the relative risk would be predicted to be lower.	Collaborative Group on Hormonal Factors in Breast Cancer 2019[6]
The relative risks used for MHT-combined (all) derived from the CGHFBC study reflect the risks associated with any individual formulation and dose of MHT assigned under that category. This risk is equivalent to that observed within the CGHFBC on analysis of all forms of MHT classified as 'combined type' or other.	
The relative risks used for MHT-combined (intermittent, cyclical) derived from the CGHFBC study reflect the risks associated with any individual formulation and dose of MHT assigned under that category. This risk is equivalent to that observed within the CGHFBC on analysis of all forms of MHT classified as 'combined type' with intermittent (cyclical) progestogen.	
The relative risks used for MHT-combined (daily, continuous) derived from the CGHFBC study reflect the risks associated with any individual formulation and dose of MHT assigned under that category. This risk is equivalent to that observed within the CGHFBC on combined analysis of all forms of MHT classified as 'combined type' with daily (continuous) progestogen.	
The relative risks used for MHT-oestrogen-only derived from the CGHFBC study reflect the risks associated with any individual formulation and dose of MHT assigned under that category. This risk is equivalent to that observed within the CGHFBC on combined analysis of all forms of MHT classified as 'E-type'.	
The relative risks derived from the CGHFBC study for <1 year MHT usage are applicable for exactly one year of MHT exposure	
The relative risks derived from the CGHFBC study for 1-4 years MHT usage are applicable for exactly five years of MHT exposure	
The relative risks derived from the CGHFBC study for 5-9 years MHT usage are applicable for exactly ten years of MHT exposure	
The relative risk for combined-intermittent (cyclical) MHT is one sixth lower and the relative risk for combined-daily (continuous) MHT is one sixth higher than the relative risk for combined-all MHT for current and past usage for all age-windows and durations of administration considered.	
The relative risk of breast cancer is constant for the duration of MHT exposure (one year/five years) as per CGHFBC estimates.	
The relative risk of breast cancer from MHT exposure persists at a constant RR up to age 70 post cessation of MHT, after which point the relative risk reverts to null (RR=1).	

The breast cancers arising due to MHT will be ER-positive breast cancers.	Kim, 2018[9]
The relative risk of breast cancer from MHT exposure is constant across different levels of family history.	Lee, 2019[10]
The relative risk of breast cancer from MHT exposure can be applied multiplicatively to the underlying annual risk of disease.	
The baseline use of MHT in the population is 0.913 (never/past), 0.011 (current oestrogen-only) and 0.076 (current other type).	
Deaths attributable to the cancer are reflected by 10-year mortality rates, i.e. deaths occurring within ten years of diagnosis. Whilst true for most solid tumours, for breast cancer due to high rates for long-term survival for metastatic disease, cancer-specific deaths may occur more than ten years post diagnosis. Deaths occurring more than ten years after disease diagnosis are not included in the mortality rates presented.	National Disease Registration Service[7]

References

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