Accepted Manuscript

British Journal of General Practice

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DOI: https://doi.org/10.3399/BJGP.2023.0327

To access the most recent version of this article, please click the DOI URL in the line above.

Received 05 July 2023
Revised 18 December 2023
Accepted 29 January 2024

Breast cancer risk assessment for prescription of Menopausal Hormone Therapy in women who have a family history of breast cancer

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Keywords: Cancer, Genetics, Epidemiology

Word count: 2409

Abstract

Background

Menopausal Hormone Therapy (MHT) can alleviate menopausal symptoms but is associated with increased risk of breast cancer (BC). MHT prescription should be preceded by individualised risk/benefit evaluation; however, data outlining the impact of family history alongside different MHT therapeutic approaches are lacking.

Aim

To quantify the risks associated with MHT use in women with varying BC family histories of i) developing and ii) dying from BC.

Design and setting

An epidemiological modelling study for women in England.

Method

We used i) background risks of BC by age and family history, ii) relative risks for BC associated with MHT use, and iii) 10-year BC-specific net mortality rates to model the risk of developing and dying from BC between the ages of 50 and 80 in women with four different BC family history profiles: 'average', 'modest', 'intermediate', and 'strong'.

Results

For a woman of 'average' family history taking no MHT, the cumulative BC risk (age 50-80) is 9.8%, and the risk of dying from the BC is 1.7%. Five years' exposure to combined-cyclical MHT (age 50-55) increases these risks to 11.0% and 1.8%, respectively. For a woman with a 'strong' family history taking no MHT, the cumulative BC risk is 19.6%, and the risk of dying is 3.2%. With 5 years of MHT (age 50-55), this increases to 22.4% and 3.5%.

Conclusion

Both family history and MHT are associated with increased risk of BC. Estimates of the risks associated with MHT for women with different family histories can support decision-making around MHT prescription.

How this fits in

Prospective analyses of longitudinal studies have enabled estimation of relative risks of breast cancer associated with different durations of exposure to and formulations of menopausal hormonal therapy (MHT). Aside from age, breast cancer family history confers the greatest contribution to breast cancer risk of the patient-reportable risk factors; risk models such as BOADICEA enable prediction of age-related breast cancer risk according to extent and pattern of breast cancer family history. We undertook integration of these two data sources in order to generate annual and 5-year risks for breast cancer incidence for the age-window 50-80 for hypothetical unaffected female consultands with different patterns of MHT exposure and different patterns of breast cancer family history, also generating predictions for breast cancer-specific death. These integrated data will enable more accurate estimates of absolute and attributable risk associated with MHT exposure for women with a family history of breast cancer, informing shared decision-making.

Introduction

Menopausal Hormone Therapy (MHT) has been widely prescribed since the 1970s for the management of symptoms associated with female menopause, but has been associated with increased risk of breast cancer, which varies by MHT preparation and duration[1–3]. However, in addition to age and MHT exposure there are a number of additional risk factors for breast cancer, of which family history is one of the strongest[4]. Administration of MHT in the context of elevated baseline breast cancer risk is of potential concern to patients and clinicians, but there are limited data available regarding impact of different patterns of MHT administration on breast cancer risk (or mortality) in the context of differing patterns of family history[5,6].

To address this, we undertook modelling for hypothetical unaffected 50-year old female consultands of four different profiles of family history (i) an 'average' woman (i.e. family history unknown), (ii) a woman with a 'modest' family history comprising a single first degree relative (FDR) affected with breast cancer at age 60, (iii) a woman with an 'intermediate' family history comprising a single FDR affected with breast cancer at age 40 and (iv) a woman with a 'strong' family history comprising two FDRs affected with breast cancer at age 50 (note that the terms 'strong', 'intermediate' and 'modest' describe family histories constructed for this analysis and do not correspond to the lifetime breast cancer risk definitions used by the National Institute for Health and Care Excellence (NICE) of 'high-risk' and 'moderate-risk'). We considered exposure to four different types of systemic (oral) MHT:

- combined oestrogen-progestagen [combined-all],
    - progestagen administered cyclically (intermittently, sequentially), eg for 10-14 days per month [combined-cyclical]
    - progestagen administered continuously (daily, bleed-free) on all days of the month [combined-continuous]
- oestrogen-only

for three different MHT exposure durations (1 year, 5 years, 10 years), evaluating (i) her likelihood of developing breast cancer over 5-years, 10-years and cumulatively up to age 80 and (ii) her likelihood of dying from a breast cancer diagnosed during this period.

Methods

See Supplementary Methods for additional detail. We estimated baseline risks (without MHT) using the validated BOADICEA V.6 breast cancer prediction model assuming the UK age-specific and calendar period-specific population incidences for invasive breast cancer[7–9]. Estimates for breast cancer relative risk associated with "current" and "past" MHT usage were obtained from the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) for four types of MHT: combined-all, combined-cyclical, combined-continuous and oestrogen-only, where the relative risks for combined-cyclical and combined-continuous MHT were calculated respectively as one sixth lower and one sixth higher than those for combined-all MHT, as per CGHFBC findings[10]. For each MHT preparation, we used the relative risks from CGHFBC relating to each of three durations of MHT administration: age 50.0 to 51.0 (1 year), age 50.0 to 55.0 (five years) and age 50.0 to 60.0 (ten years) (Supplementary Table 1). To calculate the absolute risk of breast cancer for each scenario we calculated annual breast cancer incidence; the cumulative risk of developing breast cancer between ages 50.0 and age 50.0+*x* in absence of mortality, was then calculated using standard survival analysis theory.

We used 10-year breast-cancer specific net mortality rates from 2008-2017, stratified by 10-year age-band of diagnosis, provided by NDRS (National Disease Registration Service, NHS England)[11]. We considered separately mortality rates for diagnoses of (i) all invasive breast cancers, and (ii) ER-positive invasive breast cancers. To calculate the baseline breast cancer-specific net mortality associated with the specific 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, 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 only[12]. We summed the breast cancer-specific baseline mortality with the MHT-related mortality for each decade 50.0-60.0, 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. See Supplementary Table 2 for details of additional assumptions related to the modelling.

Results

In Table 1, for varying patterns of MHT administration, we have presented the estimated cumulative risk to age 80 of developing a first breast cancer for four profiles of unaffected 50-year old female consultands and in Table 2 we have presented the corresponding risks of dying from a breast cancer diagnosed aged 50-80. For the 'average' 50-year old woman in the population (ie unknown cancer family history) with no MHT, the cumulative risk of developing breast cancer is 2.7% to age 60, 6.2% to age 70 and 9.8% to age 80, which is respectively increased to 3.5%, 7.5% and 11.0% with five years (age 50-55) and 4.5%, 8.9% and 12.4% with ten years (age 50-60) of combined-cyclical (cxxyclical) MHT.

For women with a family history of breast cancer, the baseline risk of breast cancer may be substantially increased. For example, for an unaffected 50-year-old consultand with a 'strong' family history (two FDRs diagnosed at age 50) the cumulative breast cancer risk with no MHT is 7.0% to age 60, 14.2% to age 70 and 19.6% to age 80, increasing respectively to 9.1%, 17.2% and 22.4% with five years (age 50-55) and to 11.3%, 20.1% and 25.2% for ten years (50-60 years) of combined-cyclical MHT. Therefore, five / ten years of MHT usage confers an extra 1.3% / 2.7% of absolute breast cancer risk to the woman of 'average' family history to age 70, but 3.0% / 5.9% to the woman with a 'strong' family history.

The baseline risk of dying from a breast cancer diagnosed age 50-80 is 1.7% / 1.8% / 2.0% (Table 2) for the woman of 'average' family history with no MHT / 5 years MHT / 10 years MHT (combined-cyclical). For the woman with the 'strong' family history these risks are 3.2%/3.5%/3.8%. Thus, for illustration, for 343 women with a 'strong' family history, approximately eleven would die from breast cancer diagnosed age 50-80 if none were taking MHT; if all women took five years of combined cyclical MHT then one additional woman of the 343 would die.

Compared to combined MHT, the relative risk is more modest for oestrogen-only MHT (Supplementary Table 1,Table 1a), meaning the estimates of cumulative absolute risk of breast cancer with administration of oestrogen-only MHT for those with a family history are also more modestly increased. For a 50-year-old woman with a 'strong' family history, her breast cancer risk to age 70 is increased from 14.2% (no MHT) to 15.8% / 16.6% (five/ten years of oestrogen-only MHT), as compared to 17.2% / 20.1% (for five/ten years of combined cyclical MHT). Cyclical versus continuous progestagen administration also makes a substantial difference (Supplementary Table 1, Table 1b): for the unaffected 50-year-old consultand with a 'strong' family history having five years of MHT age 50-55, the risk of breast cancer by age 70 is estimated to be 17.2% (cyclical) versus 18.3% (continuous), as compared to 14.2% with no MHT.

Discussion

Summary

From the meta-analysis of the prospective epidemiological studies in the CGHFBC study, MHT increased the relative risk of breast cancer most markedly during the exposed period ("current usage"). However, breast cancer risk remains elevated for a subsequent "legacy period" following cessation of MHT, with the magnitude relative risk during this time influenced by the duration of MHT exposure ("past usage")[10]. Thus, the duration of MHT usage has a dual effect, firstly accruing risk for longer due to "current usage" but also influencing the magnitude of relative risk applied during the legacy period (for "past usage"). The impact of family history is greater at younger ages. This greater family-history related relative risk will therefore typically coincide with the greater relative risk for "current usage" of MHT, if administered at typical timing of menopause (about age 50). However, the baseline *absolute* risk of breast cancer is relatively lower during the 50-60 decade (particularly between the ages of 50 and 55) compared to age 60-80. Therefore, the increase in absolute risk of breast cancer is comparatively modest for five years of MHT administered age 50-55 even for women with a 'strong' family history. Indeed, it was the prolonged MHT administration to women in their sixties and seventies underpinning the higher rates of observed breast cancers and accordant premature discontinuation of the Women's Health Initiative, which triggered a concomitant halving of MHT usage in the early 2000s[2]. The breast cancer risk also varies by preparation: risks are significantly lower for oestrogen-only MHT but the conommitant elevation in risk of endometrial cancer renders this option unsuitable except in women who have undergone hysterectomy[1]. The risk is also reduced via cyclical rather than continuous administration of progestagens[10].

Furthermore, breast cancer is typically associated with comparatively good prognosis, especially for hormone-receptor positive disease, the subtype associated with MHT administration[12]. For a woman of ‘average’ family history and a woman with the ‘strong’ family history, administration of five years of combined cyclical MHT will respectively increase their absolute risk of dying from a breast cancer (diagnosed 50-80) of 0.1% and 0.3% compared to no MHT.

Strengths and limitations

For the impact of MHT usage on breast cancer risk, we utilised estimates for relative risks of breast cancer calculated from collaborative analysis of 24 prospective studies of MHT usage involving 108,647 cases of female breast cancer, as this represented the largest and most detailed analysis identified. However, whilst broadly similar, other analyses have reported some differences in effect sizes.

A number of assumptions were required for modelling the risks for the different patterns of MHT administration and are presented in Supplementary Table 2. These include assumptions that the estimates of breast cancer relative risk derived from the CGHFBC (i) were constant across a delineated period of “current usage” of MHT (ii) were constant across a subsequent period of “past usage” to age 70 and (iii) that “legacy risk” stopped at age 70. The MHT-associated risks were derived from data comprising a range of MHT preparations; subgroup analysis has enabled generation of metrics for two major groups (combined and oestrogen-only), along with estimation of differences within combined preparations for cyclical versus continuous progestagen administration. Lower risks have been reported for more specific preparations, for example those containing dydrogesterone and micronized progestagens (body-identical or non-synthetic), but insufficient resolution is available to allow analyses by different durations of exposure, and for current versus past risk[10,13]. We also did not have available data by which to evaluate non-oral MHT preparations, for example transdermal oestrogens or progestagen-releasing hormonal intrauterine devices. In particpants included in the CGHFBC, <1% reported co-use of progestagen-releasing intrauterine device during the study or preceding five years, suggesting cross-contamination of these data for reported oestrogen-only MHT usage is likely to be limited.

The assumed baseline breast cancer risks for different family histories were based on modelling of familial breast cancer using segregation analysis methodologies and thus are not directly measured. However, the BOADICEA model has been extensively validated in independent prospective studies for predicting breast cancer risk on the basis of cancer family history, and is recommended for this purpose by The National Institute for Health and Care Excellence[7,14,15]. We assumed that the effect of MHT and family history act multiplicatively on risk, which fits the retrospective risk modelling of MHT for validation of the BOADICEA and Tyrer-Cuzick models. Notably, the only interaction reported in the CGHFBC was that between adiposity and risk of oestrogen-only MHT[10]. We also assume for excess breast cancers arising due the MHT that the mortality rates are those for ER-positive cancers, for which survival is better than other lower frequency breast cancer subtypes.

We did not investigate more extensive patterns of family history and did not consider the effects of other breast cancer risk factors such as breast density, body mass index (BMI), alcohol consumption and physiological endocrinological factors (such as age of menarche, number of pregnancies and duration of lactation). Therefore the estimates presented would be applicable to an average woman in the population with respect to these variables. We were not able to focus on subgroups delineated by ethnicity: by which baseline breast cancer risk, breast cancer mortality and MHT usage are reported to vary. Furthermore, we have not considered the impact of carrying pathogenic variants in breast cancer susceptibility genes such as BRCA1 and BRCA2, but such women would be typically managed in Clinical Genetics clinics. We restricted our analyses to a limited number of scenarios of MHT administration with regard to age of initiation and duration of exposure. We present risks up to age 80

because of proximity to median life expectancy (nevertheless approximately 20% of all breast cancers are diagnosed beyond the age of 80)[11]. We also focus exclusively on the MHT-associated risk of breast cancer as this is related to breast cancer family history: we do not consider the other risks associated with MHT, for example thrombo-embolism, cardiovascular disease or ovarian cancer.

Comparison with existing literature

For comprehensive individual breast cancer risk estimation, incorporation of the specific individual details of family history, genetic testing, breast density, BMI and other factors is required for which the IBIS (Tyrer-Cuzick) tool allows incorporation of both past and proposed future MHT usage whilst the CanRisk (BOADICEA) interactive tool considers past and current MHT usage only[16–18]. However, these are dynamic tools, designed for interactive individual-patient level use. None currently allow for the range of MHT formulations and durations of use considered here. These tools focus only on incidence and do not consider breast cancer-specific mortality.

Implications for research and/or practice

It is potentially challenging for patients to interpret complex data on risk. A relative risk may sound substantial, but the change in absolute risk may be modest if the baseline risk is low. A patient's perception of risk will potentially be influenced by individual, cultural and experiential factors and is inevitably subjective and context-dependent. Some patients may be interested in the shorter-term disease risk over the next five or ten years. Other patients may wish to contextualise this risk in terms of risk over a lifetime (or at least up to age 80). Some women with a family history may see the additional MHT-related risk as modest in comparison to the baseline risk. Others may seek to avoid any further increase in risk from modifiable factors, especially if they are at a very high baseline risk due to family history. Our data illustrate the comparatively modest risks of breast cancer incidence and mortality associated with a single year of MHT administration, even for those with a 'strong' family history. These data may be reassuring for women suffering severe menopausal symptoms who may wish to first explore the extent of symptom mitigation that is achievable. In future, patients and clinicians may benefit from higher resolution data covering different preparations of oestrogen and progestagen (in particular non-systemic routes).

Conclusion

Those with a significant ('strong') family history of the disease have a substantially increased baseline risk of developing breast cancer. However, most of the breast cancer incidence and mortality for this group will be attributable to their baseline risk rather than from the addition of MHT taken at age 50, even with a combined continuous preparation and even if taken for ten years. Symptoms of menopause can be highly disabling: the near-term mitigation may be of high value compared against hypothetical possibility of future disease, even for a woman with a significant ('strong') family history. Many people have limited understanding of the variability of disease-specific fatality for different cancer types: it may thus be of value to communicate the likelihood of dying from breast cancer as distinct from the likelihood of developing the disease.

Overall, these illustrations of cumulative risk of breast cancer and concomitant impact on breast cancer-specific mortality for different patterns of MHT exposure and family history will be informative for medical practitioners and patient in joint-decision making regarding MHT prescription.

Ethical approval

Not applicable.

Funding

C.H. acknowledges funding from a Wellcome Trust Clinical Research Training Fellowship (203924/Z/16/Z). H.H., K.S., M.T., D.G.E., A.C.A. and C.T. acknowledge funding from Cancer Research UK Award C61296/A27223. MT is supported by the NIHR Cambridge Biomedical Research Centre (NIHR203312).

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Cumulative risk of developing breast cancer from age 50.0-80.0, according to family history and MHT usage. Cumulative risks are presented: the proportion of individuals expected to develop breast cancer from age 50.0 to the current age specified. Family history parameters include the number of first degree relatives affected by breast cancer (one or two) and their age at diagnosis (40, 50, or 60). MHT use parameters include type of MHT used and age of use. **Table 1a:** MHT types: oestrogen-only and combined-all. **Table 1b:** MHT types: combined-continuous and combined-cyclical

	MHT Type	Current age	**51.0**	**52.0**	**53.0**	**54.0**	**55.0**	**60.0**	**65.0**	**70.0**	**75.0**	**80.0**	Likelihood of developing breast cancer age 50-80. One in:	Likelihood of developing breast cancer age 50-80 attributable to MHT. One in:
		Population risk	**0.3%**	**0.5%**	**0.8%**	**1.0%**	**1.3%**	**2.8%**	**4.4%**	**6.3%**	**8.1%**	**9.9%**	10.1	
Average woman	None	No MHT	**0.2%**	**0.5%**	**0.7%**	**1.0%**	**1.2%**	**2.7%**	**4.3%**	**6.2%**	**8.0%**	**9.8%**	10.2	
	Oestrogen only	MHT used age 50.0-51.0	0.3%	0.6%	0.8%	1.1%	1.3%	2.9%	4.6%	6.6%	8.4%	10.2%	9.8	256
		MHT used age 50.0-55.0	0.3%	0.6%	0.9%	1.3%	1.5%	3.1%	4.9%	6.9%	8.7%	10.5%	9.5	148
		MHT used age 50.0-60.0	0.3%	0.6%	0.9%	1.3%	1.5%	3.3%	5.1%	7.3%	9.0%	10.8%	9.2	98
	Combined - all types	MHT used age 50.0-51.0	0.3%	0.5%	0.7%	1.1%	1.3%	2.9%	4.6%	6.6%	8.4%	10.2%	9.8	256
		MHT used age 50.0-55.0	0.3%	0.8%	1.1%	1.6%	1.9%	3.7%	5.5%	7.7%	9.5%	11.3%	8.9	67
		MHT used age 50.0-60.0	0.3%	0.8%	1.1%	1.6%	1.9%	4.8%	6.9%	9.4%	11.2%	12.9%	7.7	32
Modest Family History (Affected FDR age 60)	None	No MHT	**0.4%**	**0.8%**	**1.2%**	**1.6%**	**2.0%**	**4.3%**	**6.7%**	**9.3%**	**11.7%**	**13.8%**	7.2	
	Oestrogen only	MHT used age 50.0-51.0	0.5%	0.9%	1.4%	1.8%	2.2%	4.6%	7.2%	9.9%	12.3%	14.4%	6.9	170
		MHT used age 50.0-55.0	0.5%	1.0%	1.5%	2.0%	2.6%	5.0%	7.6%	10.4%	12.7%	14.8%	6.7	98
		MHT used age 50.0-60.0	0.5%	1.0%	1.5%	2.0%	2.6%	5.3%	8.0%	10.9%	13.2%	15.3%	6.5	66
	Combined - all types	MHT used age 50.0-51.0	0.5%	0.8%	1.3%	1.7%	2.1%	4.6%	7.1%	9.8%	12.3%	14.4%	6.9	170
		MHT used age 50.0-55.0	0.6%	1.3%	1.9%	2.5%	3.2%	5.9%	8.6%	11.6%	14.0%	16.0%	6.2	45
		MHT used age 50.0-60.0	0.6%	1.3%	1.9%	2.5%	3.2%	7.6%	10.7%	14.1%	16.4%	18.4%	5.4	22
Intermediate Family History (Affected FDR age 40)	None	No MHT	**0.5%**	**1.0%**	**1.5%**	**2.1%**	**2.6%**	**5.4%**	**8.4%**	**11.5%**	**14.1%**	**16.4%**	6.1	
	Oestrogen only	MHT used age 50.0-51.0	0.7%	1.2%	1.7%	2.3%	2.9%	5.8%	9.0%	12.3%	14.8%	17.1%	5.8	140
		MHT used age 50.0-55.0	0.6%	1.3%	1.9%	2.7%	3.3%	6.3%	9.5%	12.8%	15.4%	17.6%	5.7	80
		MHT used age 50.0-60.0	0.6%	1.3%	1.9%	2.7%	3.3%	6.7%	10.0%	13.4%	16.0%	18.2%	5.5	55
	Combined - all types	MHT used age 50.0-51.0	0.7%	1.1%	1.6%	2.2%	2.8%	5.7%	8.9%	12.1%	14.8%	17.1%	5.8	140
		MHT used age 50.0-55.0	0.8%	1.6%	2.4%	3.3%	4.1%	7.4%	10.8%	14.4%	16.9%	19.1%	5.2	37
		MHT used age 50.0-60.0	0.8%	1.6%	2.4%	3.3%	4.1%	9.5%	13.3%	17.3%	19.7%	21.9%	4.6	18

Strong Family History (Two affected FDR age 50)	None	No MHT	**0.7%**	**1.3%**	**2.0%**	**2.7%**	**3.4%**	**7.0%**	**10.6%**	**14.2%**	**17.1%**	**19.6%**	5.1	
	Oestrogen only	MHT used age 50.0-51.0	0.9%	1.6%	2.3%	3.0%	3.8%	7.6%	11.4%	15.1%	18.0%	20.5%	4.9	114
		MHT used age 50.0-55.0	0.9%	1.7%	2.6%	3.4%	4.3%	8.2%	12.0%	15.8%	18.7%	21.1%	4.7	66
		MHT used age 50.0-60.0	0.9%	1.7%	2.6%	3.4%	4.3%	8.6%	12.6%	16.6%	19.4%	21.8%	4.6	45
	Combined - all types	MHT used age 50.0-51.0	0.9%	1.4%	2.1%	2.9%	3.6%	7.4%	11.2%	15.0%	18.0%	20.5%	4.9	114
		MHT used age 50.0-55.0	1.1%	2.1%	3.2%	4.3%	5.4%	9.5%	13.6%	17.7%	20.5%	22.9%	4.4	30
		MHT used age 50.0-60.0	1.1%	2.1%	3.2%	4.3%	5.4%	12.2%	16.8%	21.3%	23.9%	26.2%	3.8	15

Table 1b.

	MHT Type	Current age	**51.0**	**52.0**	**53.0**	**54.0**	**55.0**	**60.0**	**65.0**	**70.0**	**75.0**	**80.0**	Likelihood of developing breast cancer age 50-80. One in:	Likelihood of developing breast cancer age 50-80 attributable to MHT. One in:
		Population risk	**0.3%**	**0.5%**	**0.8%**	**1.0%**	**1.3%**	**2.8%**	**4.4%**	**6.3%**	**8.1%**	**9.9%**	10.1	
Average woman	None	No MHT	**0.2%**	**0.5%**	**0.7%**	**1.0%**	**1.2%**	**2.7%**	**4.3%**	**6.2%**	**8.0%**	**9.8%**	10.2	
	Combined - continuous	MHT used age 50.0-51.0	0.3%	0.5%	0.7%	1.1%	1.3%	2.9%	4.6%	6.6%	8.5%	10.3%	9.8	219
		MHT used age 50.0-55.0	0.3%	0.8%	1.2%	1.7%	2.0%	3.8%	5.7%	8.0%	9.8%	11.5%	8.7	58
		MHT used age 50.0-60.0	0.3%	0.8%	1.2%	1.7%	2.0%	5.2%	7.4%	10.0%	11.7%	13.4%	7.5	28
	Combined - cyclical	MHT used age 50.0-51.0	0.3%	0.5%	0.7%	1.0%	1.3%	2.8%	4.5%	6.5%	8.3%	10.1%	9.9	307
		MHT used age 50.0-55.0	0.3%	0.7%	1.0%	1.5%	1.8%	3.5%	5.3%	7.5%	9.3%	11.0%	9.1	81
		MHT used age 50.0-60.0	0.3%	0.7%	1.0%	1.5%	1.8%	4.5%	6.5%	8.9%	10.7%	12.4%	8.1	38
Modest Family History (Affected FDR age 60)	None	No MHT	**0.4%**	**0.8%**	**1.2%**	**1.6%**	**2.0%**	**4.3%**	**6.7%**	**9.3%**	**11.7%**	**13.8%**	7.2	
	Combined - continuous	MHT used age 50.0-51.0	0.5%	0.9%	1.3%	1.7%	2.1%	4.6%	7.2%	9.9%	12.4%	14.5%	6.9	146
		MHT used age 50.0-55.0	0.7%	1.4%	2.0%	2.7%	3.4%	6.1%	9.0%	12.0%	14.3%	16.4%	6.1	39
		MHT used age 50.0-60.0	0.7%	1.4%	2.0%	2.7%	3.4%	8.1%	11.4%	14.9%	17.1%	19.1%	5.2	19
	Combined - cyclical	MHT used age 50.0-51.0	0.5%	0.8%	1.3%	1.7%	2.1%	4.5%	7.0%	9.7%	12.2%	14.3%	7.0	204
		MHT used age 50.0-55.0	0.6%	1.2%	1.8%	2.4%	3.0%	5.6%	8.3%	11.2%	13.6%	15.7%	6.4	54
		MHT used age 50.0-60.0	0.6%	1.2%	1.8%	2.4%	3.0%	7.0%	10.1%	13.3%	15.6%	17.6%	5.7	26
Intermediate Family History (Affected FDR age 40)	None	No MHT	**0.5%**	**1.0%**	**1.5%**	**2.1%**	**2.6%**	**5.4%**	**8.4%**	**11.5%**	**14.1%**	**16.4%**	6.1	
	Combined - continuous	MHT used age 50.0-51.0	0.7%	1.1%	1.6%	2.2%	2.8%	5.8%	9.0%	12.3%	15.0%	17.2%	5.8	120
		MHT used age 50.0-55.0	0.8%	1.7%	2.5%	3.5%	4.4%	7.7%	11.2%	14.8%	17.3%	19.6%	5.1	32
		MHT used age 50.0-60.0	0.8%	1.7%	2.5%	3.5%	4.4%	10.1%	14.1%	18.2%	20.6%	22.8%	4.4	16
	Combined - cyclical	MHT used age 50.0-51.0	0.6%	1.0%	1.6%	2.2%	2.7%	5.7%	8.8%	12.0%	14.7%	17.0%	5.9	168
		MHT used age 50.0-55.0	0.7%	1.5%	2.2%	3.1%	3.9%	7.0%	10.4%	13.9%	16.4%	18.7%	5.4	44
		MHT used age 50.0-60.0	0.7%	1.5%	2.2%	3.1%	3.9%	8.8%	12.5%	16.4%	18.8%	21.0%	4.8	22

Strong Family History (Two affected FDR age 50)	None	No MHT	**0.7%**	**1.3%**	**2.0%**	**2.7%**	**3.4%**	**7.0%**	**10.6%**	**14.2%**	**17.1%**	**19.6%**	5.1	
	Combined - continuous	MHT used age 50.0-51.0	1.0%	1.4%	2.1%	2.9%	3.6%	7.5%	11.3%	15.1%	18.2%	20.6%	4.8	98
		MHT used age 50.0-55.0	1.2%	2.2%	3.4%	4.5%	5.7%	9.9%	14.1%	18.3%	21.1%	23.5%	4.3	26
		MHT used age 50.0-60.0	1.2%	2.2%	3.4%	4.5%	5.7%	13.0%	17.7%	22.4%	25.0%	27.3%	3.7	13
	Combined - cyclical	MHT used age 50.0-51.0	0.9%	1.4%	2.1%	2.8%	3.6%	7.3%	11.1%	14.9%	17.9%	20.3%	4.9	137
		MHT used age 50.0-55.0	1.0%	1.9%	3.0%	4.0%	5.1%	9.1%	13.1%	17.2%	20.0%	22.4%	4.5	36
		MHT used age 50.0-60.0	1.0%	1.9%	3.0%	4.0%	5.1%	11.3%	15.8%	20.1%	22.8%	25.2%	4.0	18

Table 2. Cumulative risk of death from breast cancer from age 50-80, according to family history and MHT usage. Risks of breast cancer specific death are presented: the proportion of individuals expected to die within ten years from breast cancer diagnosed age 50.0-80.0 Family history parameters include the number of first degree relatives affected by breast cancer (one or two) and their age at diagnosis (40, 50, or 60). MHT use parameters include type of MHT used and age of use. **Table 2a:** MHT types: oestrogen-only and combined-all. **Table 2b:** MHT types: combined-continuous and combined-cyclical

Family history of unaffected consultand	MHT use		For breast cancer diagnosed age 50-80				
	Type of MHT	Age of use	Cumulative risk of BC diagnosis	Total risk of breast cancer specific death (%, likelihood)		Absolute increase in risk of breast cancer specific death due to MHT compared to no MHT (%, likelihood)	
Average woman	None	No MHT	9.8%	**1.7%**	1 in 58		
	Oestrogen only	MHT used age 50.0-51.0	10.2%	**1.8%**	1 in 57	0.04%	1 in 2493
		MHT used age 50.0-55.0	10.5%	**1.8%**	1 in 56	0.07%	1 in 1406
		MHT used age 50.0-60.0	10.8%	**1.8%**	1 in 55	0.11%	1 in 940
	Combined - all types	MHT used age 50.0-51.0	10.2%	**1.8%**	1 in 57	0.04%	1 in 2376
		MHT used age 50.0-55.0	11.3%	**1.9%**	1 in 53	0.16%	1 in 642
		MHT used age 50.0-60.0	12.9%	**2.0%**	1 in 49	0.33%	1 in 305
Modest Family History (Affected FDR age 60)	None	No MHT	13.8%	**2.3%**	1 in 43		
	Oestrogen only	MHT used age 50.0-51.0	14.4%	**2.4%**	1 in 42	0.06%	1 in 1648
		MHT used age 50.0-55.0	14.8%	**2.5%**	1 in 41	0.11%	1 in 936
		MHT used age 50.0-60.0	15.3%	**2.5%**	1 in 40	0.16%	1 in 635
	Combined - all types	MHT used age 50.0-51.0	14.4%	**2.4%**	1 in 41	0.06%	1 in 1551
		MHT used age 50.0-55.0	16.0%	**2.6%**	1 in 39	0.23%	1 in 429
		MHT used age 50.0-60.0	18.4%	**2.8%**	1 in 35	0.48%	1 in 208
Intermediate Family History (Affected FDR age 40)	None	No MHT	16.4%	**2.7%**	1 in 37		
	Oestrogen only	MHT used age 50.0-51.0	17.1%	**2.8%**	1 in 36	0.07%	1 in 1361
		MHT used age 50.0-55.0	17.6%	**2.9%**	1 in 35	0.13%	1 in 761
		MHT used age 50.0-60.0	18.2%	**2.9%**	1 in 34	0.19%	1 in 522
	Combined - all types	MHT used age 50.0-51.0	17.1%	**2.8%**	1 in 36	0.08%	1 in 1281
		MHT used age 50.0-55.0	19.1%	**3.0%**	1 in 33	0.29%	1 in 350
		MHT used age 50.0-60.0	21.9%	**3.3%**	1 in 30	0.58%	1 in 173

Strong Family History (Two affected FDR age 50)	None	No MHT	19.6%	**3.2%**	1 in 31		
	Oestrogen only	MHT used age 50.0-51.0	20.5%	**3.3%**	1 in 30	0.09%	1 in 1108
		MHT used age 50.0-55.0	21.1%	**3.4%**	1 in 30	0.16%	1 in 621
		MHT used age 50.0-60.0	21.8%	**3.4%**	1 in 29	0.23%	1 in 428
	Combined - all types	MHT used age 50.0-51.0	20.5%	**3.3%**	1 in 30	0.10%	1 in 1037
		MHT used age 50.0-55.0	22.9%	**3.6%**	1 in 28	0.35%	1 in 286
		MHT used age 50.0-60.0	26.2%	**3.9%**	1 in 26	0.70%	1 in 143

Table 2b.

Family history of unaffected consultand	MHT use		For breast cancer diagnosed age 50-80				
	Type of MHT	Age of use	Cumulative risk of BC diagnosis	Total risk of breast cancer specific death (%, likelihood)		Absolute increase in risk of breast cancer specific death due to MHT compared to no MHT (%, likelihood)	
Average woman	None	No MHT	9.8%	1.7%	1 in 58		
	Combined - continuous	MHT used age 50.0-51.0	10.3%	1.8%	1 in 57	0.0%	1 in 2038
		MHT used age 50.0-55.0	11.5%	1.9%	1 in 53	0.2%	1 in 551
		MHT used age 50.0-60.0	13.4%	2.1%	1 in 48	0.4%	1 in 262
	Combined - cyclical	MHT used age 50.0-51.0	10.1%	1.8%	1 in 57	0.0%	1 in 2851
		MHT used age 50.0-55.0	11.0%	1.8%	1 in 54	0.1%	1 in 770
		MHT used age 50.0-60.0	12.4%	2.0%	1 in 50	0.3%	1 in 365
Modest Family History Affected FDR age 60	None	No MHT	13.8%	2.3%	1 in 43		
	Combined - continuous	MHT used age 50.0-51.0	14.5%	2.4%	1 in 41	0.1%	1 in 1331
		MHT used age 50.0-55.0	16.4%	2.6%	1 in 38	0.3%	1 in 369
		MHT used age 50.0-60.0	19.1%	2.9%	1 in 34	0.6%	1 in 179
	Combined - cyclical	MHT used age 50.0-51.0	14.3%	2.4%	1 in 42	0.1%	1 in 1861
		MHT used age 50.0-55.0	15.7%	2.5%	1 in 39	0.2%	1 in 514
		MHT used age 50.0-60.0	17.6%	2.7%	1 in 36	0.4%	1 in 249
Intermediate Family History Affected FDR age 40	None	No MHT	16.4%	2.7%	1 in 37		
	Combined - continuous	MHT used age 50.0-51.0	17.2%	2.8%	1 in 35	0.1%	1 in 1099
		MHT used age 50.0-55.0	19.6%	3.1%	1 in 33	0.3%	1 in 301
		MHT used age 50.0-60.0	22.8%	3.4%	1 in 29	0.7%	1 in 149
	Combined - cyclical	MHT used age 50.0-51.0	17.0%	2.8%	1 in 36	0.1%	1 in 1536
		MHT used age 50.0-55.0	18.7%	3.0%	1 in 34	0.2%	1 in 419
		MHT used age 50.0-60.0	21.0%	3.2%	1 in 31	0.5%	1 in 207
Strong Family History Two affected FDR age 50	None	No MHT	19.6%	3.2%	1 in 31		
	Combined - continuous	MHT used age 50.0-51.0	20.6%	3.3%	1 in 30	0.1%	1 in 890
		MHT used age 50.0-55.0	23.5%	3.6%	1 in 28	0.4%	1 in 246
		MHT used age 50.0-60.0	27.3%	4.0%	1 in 25	0.8%	1 in 123

	Combined - cyclical	MHT used age 50.0-51.0	20.3%	3.3%	1 in 30	0.1%	1 in 1243
		MHT used age 50.0-55.0	22.4%	3.5%	1 in 29	0.3%	1 in 343
		MHT used age 50.0-60.0	25.2%	3.8%	1 in 26	0.6%	1 in 170