Association between menopausal hormone therapy, mammographic density and breast cancer risk: results from the E3N cohort study

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Abstract

BACKGROUND: Menopausal hormone therapy (MHT) is a risk factor for breast cancer (BC). Evidence suggests that its effect on BC risk could be partly mediated by mammographic density. The aim of this study is to investigate the relationship between MHT, mammographic density and BC risk using data from a prospective study.

METHODS: The data analyzed refer to a case-control study nested into the French cohort E3N and include 453 cases and 453 matched controls. A quantitative measure of mammographic density, a detailed history of MHT use during follow-up and information on potential confounders were available for all women. The association of mammographic density with MHT duration and time since last use was evaluated by linear regression models. Mediation modelling techniques were applied to estimate under the hypothesis of a causal model the proportion of the effect of MHT on BC risk mediated by percent mammographic density for BC overall and by ER/PR status.

RESULTS: Mammographic density was higher in current (mean percent mammographic density 33%; 95% CI: 31–35%) than in former (29%; 95% CI 27% to 31) and never users (24%; 95% CI, 22–26%). Mammographic density increased with the duration of MHT within one year of therapy and reached a steady state thereafter. After discontinuation of the therapy, mammographic density decreased with time since last use and reached values similar to those of never users after 8 years. The OR of BC for current versus never MHT users, adjusted for age, year of birth, menopausal status at baseline and BMI, was 1.67 (95% CI, 1.04 to 2.68). The proportion of effect mediated by percent mammographic density was 34% on the log scale for any BC and became 48% when the correlation between BMI and percent mammographic density was accounted for. These results are limited to hormone receptor positive BCs.

CONCLUSIONS: Our results suggest that under a causal model the effect of MHT on BC risk was partially mediated by MD that appeared to be modified by MHT for up to 8 years after MHT termination.

Background

Mammographic density (MD), the area of the breast that appears white on a mammogram, is one of the strongest risk factors for breast cancer (BC) in both pre- and postmenopausal women: a meta-analysis of 13 case-control studies estimated a 40% and 50% increased risk for one standard deviation increase of absolute and percent dense area, respectively [1]. Longitudinal studies have shown that MD decreases with age, with the strongest decline occurring at the menopausal transition [2–4]. Menopausal hormone therapy (MHT) can be prescribed to women to balance estrogen depletion occurring at menopause and has the effect of enhancing the level of MD [5]. One of the most concerning side effects of MHT is the increased risk of hormone-related cancer, including breast (for estrogen-progestagen MHT) and endometrial cancer (for estrogen alone MHT) [6]. A recent pooled analysis on more than 130 000 postmenopausal BC cases diagnosed within 58 prospective studies concluded that MHT increased BC risk of current users even during the first 1–4 years and was still persistent 10 years after stopping [7]. The same pooled analysis

reported an increased risk associated to either estrogen-progestagen and estrogen alone, with a slightly higher effect of the first formulation.

Both observational and intervention studies have shown that mammographic density increases with MHT and the effect is stronger for estrogen plus progestin use than for estrogens alone [8]. Evidence suggests that the proportion of the effect of MHT on BC risk mediated by its action on mammographic density varies from 30–100% [8,9], but the effect of patterns of MHT use on the mediation mechanisms has not yet been investigated.

The aim of our work was to study the association between patterns of use of MHT and MD to better understand their independent and mediated effect on BC risk. For our analyses, we have used data of postmenopausal women from a BC case-control study nested within the French cohort E3N [10].

Methods

STUDY POPULATION

Data are from 906 women older than 55 years at the date of mammogram in the BC case-control study nested within the French E3N cohort [11]; the age of 55 years was chosen as proxy for postmenopausal status. Details of the nested case-control study are provided elsewhere [10]. Briefly, invasive adenocarcinomas of the breast (International Classification of Diseases for Oncology codes C50.0-C50.9) diagnosed between 1990 and 2010 with known laterality and at least one mammogram taken between baseline and diagnosis were matched using a density sampling procedure to women of the cohort BC-free at the age at diagnosis of the corresponding case (reference age); matching factors also included year of birth (±3 years) and menopausal status at baseline. Detailed information about demographic characteristics, lifestyle and reproductive history was available for all women in the cohort from structured questionnaires collected at baseline and every 2–3 years during follow-up.

The pattern of use of MHT and oral contraceptives during the follow-up and up to the mammogram, including status of use at mammogram (never versus current versus former), type of therapy (estrogen alone versus estrogen plus progestagen), duration of use for current users and time since last use for former users, was calculated from data collected from the repeated questionnaires.

ASSESSMENT OF MAMMOGRAPHIC DENSITY

Women in the nested case-control study had their mammograms retrieved. For the cases and the matching controls mammographic density was quantified from the craniocaudal image of the breast ipsilateral to the tumor that was closest and prior to the reference age. The mammographic films were digitized with an Array 2905 high-density film digitizer (Array Corporation Europe, Roden, The Netherlands) with a resolution of 300 PPI and were resized for density reading with a proportional maximal size of 800 × 400 pixels. A single reader (GM), who was blinded to case-control status, assessed total breast area and dense area (DA) in batches of 200 mammograms using a computer-assisted

technique (Cumulus, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada) [12]. Percent mammographic density (PMD) was computed as the ratio of DA to the total breast area, and non-dense area (NDA) as the difference between total breast area and DA. For quality control, a random sample of 120 images was read in duplicate with resulting intraclass correlation of 0.98 for total breast area, 0.95 for DA, and 0.96 for PMD.

STATISTICAL METHODS

To achieve normality of their distribution, PMD, DA and NDA were transformed using a square root transformation. The effect of MHT on each MD measure was estimated by fitting age-adjusted linear regression models to the transformed MD variables. First, we fitted models where MHT was categorized as never, current and former users at the time of MD measures; then, to account for pattern of use, duration for “ever users” and time since last use for “former users” were dichotomized according to their medians. Finally, we fitted polynomial models with duration and time since last use as continuous variables; the degree of the polynomial best fitting the data was identified through the Akaike’s Information Criterion (AIC). In the linear regression analyses, to account for the over-representation of BC cases in the data set compared to the general population, cases and controls were weighted by p/2 and (1-p)/2 respectively [13], where p was set to 0.08, an estimate of the prevalence of BC cases in the general population of women aged more than 55 years. We evaluated the effect of the following potential confounders: family history of BC; age at menarche; previous use of oral contraceptive; parity and lactation. Because BMI was considered as a mediator of the effect of MHT on MD, it was not included among the potential confounders. The heterogeneity of effect of the type of MHT formulation was assessed by comparing ever users of a single type of hormonal therapy to never users, after excluding women who used more than on type of MHT.

To estimate the total effect of MHT on BC risk and the component of the effect mediated by PMD we adopted two different approaches. First, the odds ratios (ORs) for BC were estimated by an unconditional logistic model adjusted for the matching variables (i.e. reference age, year of birth, menopausal status at baseline) and BMI (partial adjustment). The additional effect of family history of BC, age at menarche, use of oral contraceptive, parity and lactation as potential additional confounders was also evaluated (complete adjustment). In order to exclude the possibility that the differences between the results of the partially and completely adjusted mediation models were due the presence of missing values, both analyses were performed after excluding 48 pairs with missing values in any of the potential confounders. Second, to account for the correlation between PMD and BMI in evaluating their joint role as mediators of the effect of MHT on BC risk, we applied a modified version of the quasi-Bayesian algorithm by Imai et al. [14] described elsewhere [15]. In the application of this model, the linear relationship between the squared root transformed PMD and MHT was estimated using the weights to account for the over-representations of BC cases, as described above. The mediation analyses were conducted for the risk for all BCs and separately for hormone receptor positive (ER positive or PR positive) and hormone receptor negative (ER negative and PR negative). In both approaches, the proportion of effect mediated by PMD was calculated on the logarithmic scale ($\log(OR_{mediated})/\log(OR_{total})$) [13].

Results

STUDY POPULATION

For the 453 cases and 453 controls of the study sample, the median time between the enrolment in the E3N cohort and mammogram was 11.3 years (interquartile range (IQR): 9.0 to 13.2 years). Fifty percent of the women were born before 1939 (IQR: 1936 to 1943); median age at diagnosis of cases was 61 years (IQR: 59 to 66); the median age at mammogram was 61 years (IQR: 58 to 65 years); the median time between the mammograms and reference age in the cases was 0.2 years (IQR: 0.1 to 1.6 years). Cases had higher BMI and DA than controls (median BMI: 23.1 versus 22.8 kg/m^2, $P = 0.005$; median DA: 35 versus 29 cm^2, $P < 0.001$); no statistically significant difference was observed for NDA (median NDA: 68 versus 72 cm^2, $P = 0.36$) The proportion of MHT ever users was higher among cases than controls (0.83 vs 0.76, $P = 0.009$). When the contribution of cases and controls was weighted to properly account for their distribution in the general population, the mean BMI was 23.1 kg/m^2 (SD, 3.1 kg/m^2), the mean DA and NDA were 33 cm^2 (SD: 21) and 79 cm^2 (SD: 43) respectively, and the proportion of MHT ever users 0.76. Other characteristics of the study sample are reported in Table 1.

Table 1
Characteristics of the women.

Characteristic	All (*N* = 906)	Controls (*N* = 453)	Cases (*N* = 453)
*Reference age (yrs)**	61 (59 to 66)	61 (59 to 66)	61 (59 to 66)
*Age at mammogram (yrs)**	61 (58 to 65)	61 (58 to 65)	60 (58 to 65)
MHT at mammogram, N (%)			
Never	189 (20.9)	110 (24.3)	79 (17.4)
Current	432 (47.7)	217 (47.9)	215 (47.5)
Former, 0–2 years since last use	154 (17.0)	50 (11.0)	104 (23.0)
Former, > 2 years since last use	131 (14.5)	76 (16.8)	55 (12.1)
*BMI at mammogram (kg/m^2)**	22.9 (21.1 to 25.1)	22.8 (21.0 to 24.8)	23.1 (21.3 to 25.4)
*PMD**	32 (20 to 45)	31 (17 to 43)	35 (23 to 49)
*Dense area (cm^2)**	33 (20 to 47)	29 (17 to 42)	35 (23 to 52)
*Non-dense area (cm^2)**	70 (47 to 97)	72 (49 to 97)	68 (46 to 96)
*ER and PR status, N (%)***			
ER or PR positive			338 (85.8)
ER and PR negative			56 (14.2)
Familiarity			
No	771 (85.1)	394 (87.0)	377 (83.2)
Yes	135 (14.9)	59 (13.0)	76 (16.8)
Age of menarche (yrs)			
<12	162 (17.9)	69 (15.2)	93 (20.5)
12	244 (26.9)	125 (27.6)	119 (26.3)
>12	500 (55.2)	259 (57.2)	241 (53.2)
Use of oral contraceptives			
No	452 (49.9)	232 (51.2)	220 (48.6)

MHT: menopausal hormone therapy; BMI: body mass index; PMD: percent mammographic density; ER: estrogen receptor; PR: progesterone receptor.

*Median (interquartile range)

** Number of missing: ER/PR status,59; Parity and lactation, 51

Characteristic	All (*N* = 906)	Controls (*N* = 453)	Cases (*N* = 453)
Yes	454 (50.1)	221 (48.8)	233 (51.4)
*Parity and lactation***			
Nulliparous	116 (13.6)	59 (13.9)	57 (13.2)
Parous without lactation	205 (24.0)	94 (22.2)	111 (25.8)
Parous with lactation	534 (62.5)	271 (63.9)	263 (61.0)
MHT: menopausal hormone therapy; BMI: body mass index; PMD: percent mammographic density; ER: estrogen receptor; PR: progesterone receptor.			
*Median (interquartile range)			
** Number of missing: ER/PR status,59; Parity and lactation, 51			

ASSOCIATION BETWEEN MENOPAUSAL HORMONE THERAPY AND MAMMOGRAPHIC DENSITY

MHT use status at mammogram was significantly associated with PMD, DA and NDA ($P < 0.001$, < 0.001 and 0.006, respectively): for PMD and DA, former users had significantly higher levels than never users ($P = 0.003$ and $P = 0.005$ respectively) and significantly lower levels than current users ($P = 0.004$ and $P = 0.003$ respectively); for NDA, both former and current users had lower levels than never users, but differences were statistically significant only for current versus never users ($P = 0.001$). Table 2 shows the predicted MD values by MHT status for a woman aged 60 years. Distinguishing MHT ever users by type of MHT formulation did not improve the fit for any of the MD variables ($P = 0.86$, 0.63 and 0.67, respectively).

Table 2
Predicted mammographic measures in women 60 years old by type of menopausal hormone therapy.

		PMD (%)	DA (cm^2)	NDA (cm^2)
	N	Predicted (95% CI)	Predicted (95% CI)	Predicted (95% CI)
Never	189	24 (22 to 26)	24 (22 to 26)	78 (72 to 83)
Any MHT				
Former use	285	29 (27 to 31)	29 (26 to 31)	71 (66 to 76)
Current use	432	33 (31 to 35)	33 (31 to 35)	67 (63 to 70)
Estrogens				
Former use	13	28 (18 to 40)	25 (15 to 36)	62 (43 to 86)
Current use	17	35 (27 to 45)	34 (25 to 43)	64 (49 to 81)
Estrogens plus progestagens				
Former use	197	30 (27 to 32)	30 (27 to 33)	72 (67 to 78)
Current use	293	33 (31 to 35)	33 (31 to 35)	65 (62 to 70)

PMD: percent mammographic density; DA: dense area; NDA: non-dense area; MHT: menopausal hormone therapy.

To assess the effect of pattern of use of MHT on MD, we fitted a model including both duration and time since last use categorized according to their medians in all women (6 and 2 years, respectively). Among past users, time since last use was negatively associated to PMD ($P = 0.009$) and DA ($P < 0.001$), and positively but not significantly associated to NDA ($P = 0.24$). There was no statistically significant effect of duration on PMD, DA nor NDA (all $P > 0.05$). For none of the mammographic density variables, adding the interaction between duration and time since last use significantly improved the model. Then duration was excluded from the model. Table 3 reports the corresponding predictions of PMD, DA and NDA for a woman aged 60 years old without duration in the model. For all three MD variables, the values for past users who stopped for less than 2 years were not statistically significantly different from those of current users ($P = 0.65$ for PMD, 0.88 for DA and 0.95 for NDA), whereas the values for past user who stopped for more than 2 years were not significantly different from those of never users ($P = 0.19$, 0.39 and 0.44, respectively).

Table 3
Predicted mammographic measures in women 60 years old by pattern of menopausal hormone therapy use.

	PMD (%)	DA (cm^2)	NDA (cm^2)
	Predicted (95% CI)	Predicted (95% CI)	Predicted (95% CI)
Never	24 (22 to 26)	24 (22 to 26)	78 (72 to 83)
Current	33 (31 to 35)	33 (31 to 35)	67 (63 to 70)
Former, 0–2 yrs since last use	32 (29 to 36)	33 (29 to 37)	67 (60 to 74)
Former, > 2 yrs since last use	26 (24 to 29)	25 (23 to 28)	74 (68 to 81)
PMD: percent mammographic density; DA: dense area; NDA, non-dense area.			

For all three mammographic variables, the best polynomial model included the first-grade polynomial for duration and the second-degree polynomial for time since last use (supplementary Table S1). The trends by age of PMD, DA and NDA predicted by such models are shown in Fig. 1 for a woman never using MHT; a woman starting MHT at the age of 55 and never stopping; a woman starting at the age of 55 and stopping after 3, 6 or 8 years (second, third and forth quartiles of MHT duration). The time necessary for mammographic density transition from never to current MHT use was very short (less than one year), as indicated by the discontinuity of the predicted curve between never and current users. According to the models, for a woman starting MHT at 55 years and stopping after 3 years, the levels of PMD, DA and NDA returned to the levels of never users after approximately 8, 9 and 4 years respectively; after 8, 11 and 6 if the same woman stopped MHT after 6 years; after 8, 12 and 6 years if she stopped after 8 years.

The adjustment for additional potential confounders did not materially change any of the above estimates.

MEDIATION ANALYSIS

Considering that the effect of MHT on MD can be observed for up to 8 years after stopping (see previous section), we conducted mediation analyses only on current and never MHT users. In the partially adjusted model, the OR of BC associated with *current* versus *never* use of MHT was 1.67 (95% CI, 1.04 to 2.68); when PMD was added into the model, the OR became 1.40 (95% CI, 0.86 to 2.28) that corresponds to a 34% mediated effect on the log scale. When mediation analysis was stratified by hormone receptor status, it appeared that the association between MHT and BC risk was mainly due-to hormone receptor positive breast cancers: the OR associated to *current* use of MHT was 1.81 (95% CI, 1.05 to 3.10); when PMD was added into the model the OR became 1.46 (95% CI, 0.84 to 2.57), corresponding to 36% mediated effect. For hormone receptor negative breast cancers the association between MHT and BC was not significant, either without or with inclusion of PMD into the model (OR = 0.64, 95% CI 0.15 to 2.81, and OR = 0.57, 95% CI 0.12 to 2.70, respectively). Similar findings were obtained from the totally adjusted

regressions, where the proportion of the effect of MHT mediated by PMD was 40% for any BC and 41% for hormone positive BC.

Table 4 reports the results from the mediation model that accounted for the joint mediation effect of PMD and BMI (Pearson's correlation coefficient between square-rooted transformed PMD and BMI − 0.39, $P <$ 0.001). In the partially adjusted model, the OR associated to current use of MHT was 1.46 (95% CI, 0.42 to 2.41); the average direct effect was 1.37 (0.85 to 2.18); the average mediated effects were 1.20 (1.06 to 1.41) for PMD and 0.90 (0.78 to 0.98) for BMI. When mediation analysis was stratified by hormone receptor status, it appeared that the association between MHT and BC risk was entirely due to hormone receptor positive breast cancers: the total effect of MHT was 1.58 (0.93 to 2.64), resulting from a direct effect of 1.44 (0.85 to 2.34) and indirect effects of 1.22 (1.06 to 1.52) through PMD and 0.91 (0.78 to 0.99) through BMI. According to this model the proportion of effect mediated by PMD on the log scale was 48% for any BC cancers and 43% for hormone receptor positive BC.

No material changes were observed in the results of the mediation analysis when the models were adjusted for all potential confounders (Table 4). Qualitatively similar results were observed for MHT coded as ever versus never (supplementary Table S2).

Table 4
Mediation analysis of the effect of menopausal hormone therapy on breast cancer risk

	All	ER or PR positive	ER and PR negative
	N_{CA}=196/N_{CO}=196	N_{CA}=150/N_{CO}=150	N_{CA}=22/N_{CO}=22
Partially adjusted model*			
Total effect	1.46 (0.92 to 2.41)	1.58 (0.93 to 2.64)	0.63 (0.11 to 2.61)
Average direct effect	1.37 (0.85 to 2.18)	1.44 (0.85 to 2.34)	0.61 (0.10 to 2.48)
Average joint mediated effect	1.07 (0.92 to 1.25)	1.10 (0.93 to 1.37)	1.00 (0.48 to 2.52)
Average mediated effect by PMD	1.20 (1.06 to 1.41)	1.22 (1.06 to 1.52)	1.10 (0.61 to 2.63)
Average mediated effect by BMI	0.90 (0.78 to 0.98)	0.91 (0.78 to 0.99)	1.00 (0.49 to 1.40)
Totally adjusted model†			
Total effect	1.49 (0.89 to 2.49)	1.53 (0.91 to 2.71)	0.79 (0.14 to 2.92)
Average direct effect	1.34 (0.82 to 2.18)	1.36 (0.81 to 2.47)	0.63 (0.13 to 2.63)
Average joint mediated effect	1.09 (0.94 to 1.31)	1.11 (0.93 to 1.40)	1.18 (0.61 to 2.62)
Average mediated effect by PMD	1.23 (1.07 to 1.48)	1.26 (1.07 to 1.56)	1.20 (0.84 to 2.71)
Average mediated effect by BMI	0.89 (0.79 to 0.98)	0.90 (0.75 to 0.99)	1.00 (0.54 to 1.53)

Mediation analysis evaluating the direct and indirect effect of current versus never use of MHT on breast cancer risk, overall and by ER and PR status in presence of PMD and BMI, correlated mediators.*Model including: age and MHT at mammogram; menopausal status at baseline and year of birth. †Model including: age and MHT at mammogram; menopausal status, familiarity, parity, lactation, use of oral contraceptives at baseline; year of birth and age of menarche. ER: estrogen receptor; PR: progesterone receptor; PMD: percent mammographic density; BMI: body mass index; MHT: menopausal hormone therapy.

Discussion

The analysis of the data collected within the E3N prospective cohort showed that postmenopausal women taking MHT have higher PMD and DA and lower NDA than never users of MHT and that this difference is observed already within the first year of MHT use. Stopping MHT leads to a decrease of PMD and DA whose levels reach those of never users after more than 8 years since stopping the therapy. No heterogeneity was observed between estrogen alone and estrogen plus progestogen MHT formulations. The effect of current use of MHT on BC risk was partially direct and partially mediated by PMD and BMI; the mediated effect was entirely restricted to the hormone receptor positive tumors.

The association between MHT use and MD has been previously reported. A randomized study estimated that after one year since starting therapy PMD increased of about ten percentage point in women in the

estrogen-progestin arm, whereas no change was observed in women taking placebo [8]; this longitudinal change was comparable to our estimate of a difference of 8 percentage points in PMD (estimated from the polynomial model) between a woman aged 56 years who took MHT for 1 year and a never user 55 years old. To our knowledge, our study is the first trying to model MD in a prospective cohort of postmenopausal women by pattern of MTH use including duration of use and time since last use. Our observation that women taking MHT for less than one year had higher MD levels than never users and that the difference was observed also in those who stopped treatment less than 8 years earlier is consistent with the findings about the association between MHT and BC risk. Previous analyses of the full E3N cohort reported an effect of MHT on BC risk already in the first two years after starting [16,17]. A meta-analysis conducted on more than 100 000 BC cases from prospective studies estimated that the increased risk of BC associated with MHT in current users appeared in the first 5 years of use and almost doubled in the following 5–14 years of use; in past users, excess risk persisted even after 10 years since stopping [7].

According to our data, MD responds to MHT following a trend similar to that of BC risk, consistently with its role as mediator of the effect of MHT on BC risk. We estimated that PMD mediated between 34% and 50% of the effect of current use of MHT on MD, an effect comparable to the 31% effect reported in the Nurses' Health Study [9], but much smaller than the 100% reported in the case-control study nested within the randomized Women Health Initiative [8].

In the meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer, the increased risk of BC associated with MHT was observed for all type of MHT except vaginal estrogen and the risk was greater for estrogen plus progestogen than for estrogen alone; moreover, the risk was higher for ER positive than ER negative BCs [7]. The analyses conducted on the entire E3N cohort identified heterogeneity of the effect on BC risk of the type of MHT preparation and provided evidence for a differential effect on risk by BC subtype [17]. Our present analysis did not show evidence for heterogeneity of the effect of MHT on MD by formulation, although the number of women taking estrogen only was too small to provide an adequate power. As to the subtype of cancer, consistently with the previous observation on BC risk, we observed that PMD mediated the effect of MHT on BC risk only for hormone receptor positive BCs, but nor for hormone receptor negative BCs.

The main strengths of our study were its prospective design and the completeness of information about MHT pattern of use over a median period of time of 11 years. The richness of the information available from the E3N cohort allowed us to adjust for all known potential confounders of the relations between MHT, MD and BC risk, essential for an unbiased estimate of the mediated causal effect [18]. One limitation of our study was the small proportion of women taking estrogen alone MHT, which did not allow to properly test for a difference between estrogen alone and estrogen plus progestagen. Also, not having repeated longitudinal measures of MD made it impossible to estimate intra-individual changes in MD over time.

The use of MHT in Western countries saw a strong increase in the nineties when studies suggested its beneficial effect on postmenopausal women health [19–22]. After the first results from the Women Health Initiatives in 2002 [23] reporting an excess risk of BC and cardiovascular diseases in the estrogen plus progestin arm compared to the placebo arm, the number of MHT consumers abruptly decreased. Subsequent reanalysis of the follow-up data of the same trial and independent studies suggested that the benefits of MHT taken over menopause overcome its negative effects, resulting in an overall improved survival [24–28]. It has been estimated that in 2010 there were about 12 million users in Western countries [7]. The meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer published in 2019 provided new elements for the ongoing debate about the safety of use of MHT [7,29].

Conclusions

MD was higher in current than never users already within the first year of use; in past users, its levels reached those of never users after more than 8 years since stopping the therapy. MD mediated up to 50% of the effect of MHT on breast cancer risk.

Our results, if confirmed by independent longitudinal studies, indicate that MHT should be prescribed with caution particularly in women with high MD and suggest that monitoring MD during MHT might be a useful strategy in situations when MHT prescription is appropriate.

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All participants signed informed consent in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (Commission Nationale de l'Informatique et des Libertés), from which we obtained approval.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The dataset analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

GM, GS and LB designed the study. MF, VP, AJ and LB performed the statistical analyses. MF, VP, GS and LB prepared the original draft with suggestions from the other authors. All authors interpreted the results and read and approved the final manuscript.

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Abbreviations

AIC: Akaike's Information Criterion

BC: Breast cancer

DA: Dense area

CI: Confidence interval

IQR: Interquartile range

MD: Mammographic density

MHT: Menopausal hormone therapy

ND: Non-dense area

OR: Odds ratio

PMD: Percent mammographic density

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Figures

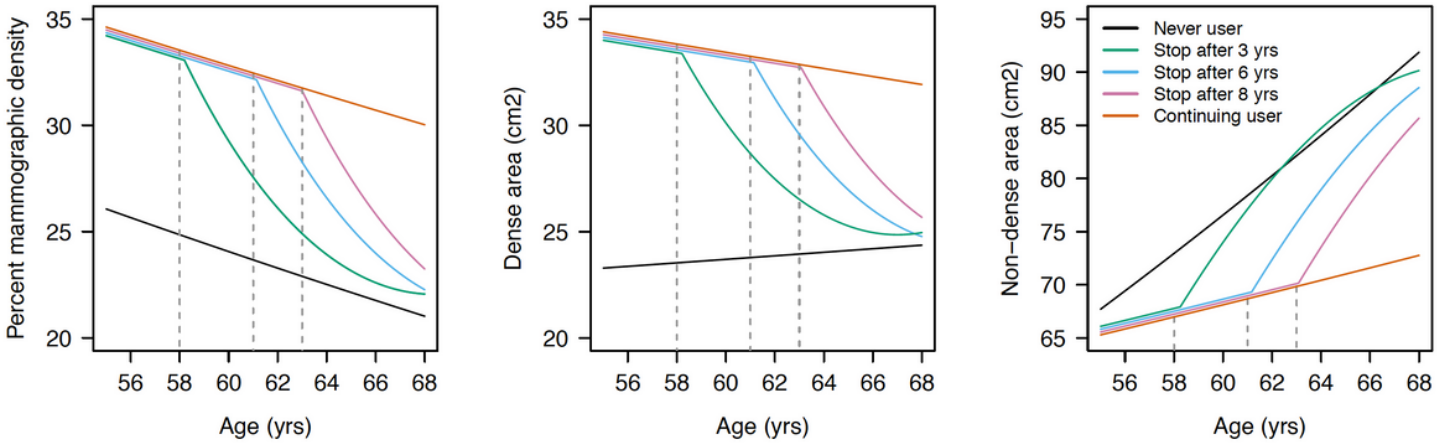

Figure 1

Trends of mammographic measures for different patterns of use of menopause hormone therapy (MHT). Trends by age of percent mammographic density, dense area and non-dense area for a hypothetical woman who never used MHT (black); one who started MHT use at the age of 55 and never stopped (orange); one who started at the age of 55 and stopped at the age of 58 (green); one who started at the age of 55 and stopped at the age of 61 (blue); one who started at the age of 55 and stopped at the age of 63 (magenta). Lines are from models including age at mammogram, MHT status (never vs ever), duration of use for ever users (continuous linear) and time since last use for past users (continuous quadratic).

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