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The V Metric, Menopausal Hormone Therapy, And Breast Cancer Risk

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ABSTRACT

Background and Aims. Long-term use of menopausal hormone therapy, typically in the form of estrogen or estrogen + progesterone, can increase the amount of dense breast tissue in women, which is associated with breast cancer. These changes are commonly measured using mammograms to calculate percent density; higher percent density is also associated with breast cancer. Newer methods of mammogram analysis look at spatial texture feature variation; these approaches are more sensitive than percent density, however the association between texture features and hormone therapy use is not well-documented. This study aims to analyze a specific texture feature, the V metric, which is a measure of the standard deviation of greyscale pixel intensity values from a mammogram image. We evaluated the V metric and its associations with both estrogen and estrogen + progesterone menopausal hormone therapy for durations of less than or equal to 5 years as well as more than 5 years. Our goal was to further establish V as a sensitive predictive measure of breast cancer.

Methods. This was a retrospective cohort study that used participant data from the Nurses' Health Study I and II. The study included 1,986 postmenopausal women that had available mammograms and menopausal hormone therapy use data. From both low and high-resolution mammograms, the V metric is computed. To evaluate the outcome variable V, linear mixed models were fit, adjusting for age, BMI, race, menopause, family history of breast cancer, personal history of benign breast disease, total breastfeeding, age at first birth, parity, age at menarche, age at menopause, physical activity, and alcohol intake. Models were then stratified by menopause type and percent mammogram density. Sensitivity analyses were conducted with the subset of mammograms that were high-resolution.

Results. Adjusting for covariates, participants that used estrogen + progesterone for more than 5 years had significantly higher mean V measures than those that used estrogen or never used menopausal hormone therapy. Participants using any form of menopausal hormone therapy for any duration had significantly higher mean V measures than never users.

Conclusions. Menopausal hormone therapy is significantly associated with higher mean V measures. Various durations of therapy can affect breast tissue physiology, leading to increases in dense tissue. This can increase risk of breast cancer. Notably, the V metric may quantify some changes that percent mammogram density does not register. Particularly in women that used estrogen + progesterone therapy for longer durations, the V metric may be a more accurate predictor of breast cancer risk. Additional evaluation of related physiological factors and their associations with the V metric will help increase its validity.

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INTRODUCTION

As menopause commences, fluctuating hormone levels (most notably estrogen) can lead to a wide range of ailments, including hot flashes, sweating, mood changes, and joint/muscle pain. In order to alleviate these symptoms, a variety of drug treatments may be prescribed, which are collectively known as Menopausal Hormone Therapy (MHT). In most cases, MHT is prescribed as a form of estrogen, either independent or in combination with another hormone, such as progesterone or, less commonly, testosterone[16]. The aim of this therapy is to increase hormone levels in a manner that can effectively reduce negative symptoms.

While MHT is often helpful in improving the wide range of symptoms and discomforts associated with menopause, research has shown that there are also long-term risks associated with its use, such as breast cancer[1,16]. This association varies for specific kinds of MHT- for instance, risk has generally been found to be higher among users of combined estrogen + progesterone formulations as opposed to estrogen alone[14]. Further, the relation between MHT use and breast cancer risk may be mitigated by other factors, such as parity, increased breastfeeding duration, and body mass index (BMI). A general explanation for the impact of MHT on breast cancer risk may be estrogen's diverse hormonal impact on physiology[4,14,15]. Effects of MHT are considerable- notably, findings have shown that MHT affects mammographic density, a measure of dense tissue (including milk glands, ducts, and supportive tissue) vs. non-dense (fatty) tissue in the breast (denoted as percent mammographic density: PMD)[10,11]. Specifically, MHT has been shown to increase dense tissue, and higher PMD is strongly associated with breast cancer risk[2,11,15]. Research on MHT, as well as PMD, has thus proven to be useful in predicting and measuring breast cancer risk. Having access to MHT and PMD information for study participants can be particularly helpful in evaluating breast cancer

risk. Fortunately, PMD is a reliable and easily accessible measure; it is derived from the relative measure of dense to non-dense tissue in a mammogram image, and many women that have undergone MHT have had a mammogram.

Recently, different approaches to analyzing mammograms have been in development. As opposed to considering a relative measure of density, the actual distribution of the dense tissue throughout the breast can be quantified. These approaches are referred to as "texture measures", as they are considering the different appearances, or "texture" of dense tissue on a 2-D mammogram. These texture measures, like PMD, have been shown to be associated with breast cancer risk[8,12]. However, they are significant because their association exists independently of percent density, meaning that they may potentially be another useful predictive tool. One specific texture measure, the V metric, was developed using data from 3 different studies at the Mayo Clinic[10]. It considers the variation of grey intensity values across the mammogram, compiling them into a summary statistic that has also been shown to be associated with breast cancer risk[12].

In the Nurses' Health Study (NHS) and NHSII, we have shown that the V metric is associated with breast cancer risk independent of PMD[17]. While there is already evidence of association between MHT and PMD, it is unknown whether MHT may influence other texture measures, such as the V metric. Understanding the relationship between MHT and the V metric will be useful for characterizing how MHT may influence breast tissue as it appears on a mammogram, as well as determining how the V metric may be predictive of breast cancer risk.

METHODS

Study Population

The NHS and NHS II are longitudinal cohort studies, with start dates in 1976 and 1989, respectively. Briefly, at baseline, the NHS enrolled 121,700 female registered nurses (RNs) with ages ranging from 30 to 55. NHS II is comprised of 116,429 RNs aged 25 to 42. Participants in both studies filled out biennial questionnaires, providing health and medical information, as well as behaviors and lifestyle factors. Participants reported any new incidence of disease, including breast cancer, in each follow-up questionnaire.

Of the participants in the main NHS and NHS II studies, individuals in blood and cheek cell collection cohorts were selected as controls in a nested case-control study of breast cancer. Specifically, 32,826 NHS participants aged 43 to 70 had blood drawn in 1989 or 1990; samples were then stored in liquid nitrogen. For NHS II, 29,611 participants aged 32-45 had blood drawn between 1996 and 1999, and samples were again stored. Across these breast cancer nested case-control studies, 1 to 2 controls were matched per breast cancer case. We attempted to collect mammograms for all participants in these nested case-control studies as close as possible to the time of blood draw date, totaling 2,137 cases and 4,346 controls.

Analyses were restricted to postmenopausal controls with measured V and key exposure covariates. We excluded 1,890 women who indicated they were premenopausal at the time of mammogram. From total controls, we also excluded women with missing values for V (n=338), MHT status (n=2,013), and age (n=0) or BMI (n=81) at the time of mammogram. Values for each missing variable are those missing from the total controls (n=4,346); there was significant overlap. After restriction, 1,986 postmenopausal women were included in the analysis, 1,547 from NHS and 439 from NHSII.

Exposure Assessment

Menopausal hormone therapy use was reported by participants on every biennial questionnaire. Using these data, we evaluated the MHT use closest to and prior to the mammogram date. Participants were assigned to one of seven categories: "Never used menopausal hormones", "Used them in any form in the past", "Current use of estrogen for MHT for less than 5 years", "Current use of estrogen for MHT for more than 5 years", "Current use of estrogen and progesterone for MHT for less than 5 years", "Current use of estrogen and progesterone for MHT for more than 5 years", or "Current use, other" (includes progesterone alone, vaginal estrogen or vaginal progesterone, estrogen and testosterone, and other unspecified combinations).

The V Metric

The V metric considers grey-scale intensity variation across the mammogram image[10]. To obtain a "V75" V metric measure, the outer 25% of the breast area is eroded in a radial direction to eliminate possible error regions- the outer region may not be considered as reliable as it is not central to compression paddles during imaging. After erosion of these outer regions, the standard deviations of the pixel values within the central region gives the V metric, which may be either negative (low) or positive (high). Mammograms included in this analysis were obtained using various equipment and had differing resolutions.

Statistical Analysis

To estimate beta coefficients (β) and 95% confidence intervals (CI) for the association between MHT status and V measure, a multivariable linear mixed model was used. All covariate information was measured at or near time of mammogram and included age (continuous), BMI (continuous), race (White, non-White), menopause type (natural vs. surgical), family history of

breast cancer (yes/no), personal history of benign breast disease (yes/no), total breastfeeding months (less than 1, 1 to 6, 7 to 12, 13 or more), age at first birth (continuous), parity (continuous), age at menarche (continuous), age at menopause (continuous), physical activity (0 to 7.5 hrs/wk, 7.5 to 15 hrs/wk, 15 to 28 hrs/wk, over 28 hrs/wk), and alcohol intake (0g/d, 0.1 to 4.9g/d, 5.0 to 14.9g/d, >15.0g/d). An initial base model included age and BMI as covariates, as both have been shown to be strongly associated with PMD and breast cancer risk[8]. All covariates were considered in the multivariable model, with covariates being selected by significance level, while also evaluating overall R^2 for each covariate addition/deletion. MHT status, age, and BMI were included in all model iterations. From potential models, the model with the lowest Schwartz Bayesian information criterion (a measure of overfitting), largest R^2, and simultaneous covariate p-value significance was chosen. The multivariable model included MHT status, age, BMI, race, family history of breast cancer, personal history of benign breast disease, total breastfeeding months, age at first birth, and parity. A multivariable + PMD model included PMD as a covariate.

Previous studies have indicated clear effects of age and BMI on PMD and texture features[8,13]. However, other factors, including those relating to menopause, have not been investigated. To determine whether type of menopause (e.g., natural vs. surgical) was an effect modifier, we ran stratified analyses and conducted separate regressions for interaction. Additionally, we conducted secondary analyses by categorizing PMD using its median (high vs. low). In sensitivity analyses, we evaluated the V metric's association using high resolution mammogram images only (N=862).

RESULTS

Participant Characteristics

Of 1,986 included women, the mean age at time of mammogram was 58.0, and the mean BMI was 26.1. The majority of women were White (95.8%), parous (90.5%), and had no family history of breast cancer (88.0%) (Table 1). Roughly half (54.2%) of women indicated natural menopause. However, as expected, women that used estrogen only MHT for <5 years and for 5+ years had much higher rates of surgical menopause (84.1% and 90.0%). Women using estrogen only MHT also had lower average ages for menopause (42.9 and 41.1, respectively), compared with never users and users of MHT formulations.

In the main age-standardized analyses, the mean V metric ranged from -0.43 to 0.07. Women that used estrogen + progesterone for less than 5 years had the greatest mean V measure (0.07), while women that never used MHT had the lowest (-0.43). In sensitivity analyses, women that used estrogen + progesterone for over 5 years had the greatest mean V measure (-0.02), while never users again had the lowest (-0.52). PMD was highest among estrogen + progesterone <5y users (32.2) and lowest among never users (23.2). Overall, the V metric was positively correlated with PMD (Pearson r=0.56). A similar correlation was observed when we limited to the high-resolution images only (Pearson r=0.50; N=862).

Menopausal Hormone Therapy

In age and BMI adjusted models, using estrogen only or estrogen + progesterone was significantly associated with higher V75 compared with never users. Participants using estrogen+ progesterone for <5y had mean V measures 0.36 greater than never users, and estrogen only <5y indicated an increase in mean V measure of 0.27. When the age and BMI model was stratified by menopause type (natural vs. surgical), the natural menopause model estimate for mean V

measure increased for estrogen+ progesterone <5y (β=0.47, 95% CI= 0.30 to 0.63), as well as for estrogen only >5y and estrogen+ progesterone >5y. When stratified by PMD (low vs. high, cutoff at median), the association for estrogen+ progesterone <5y at high PMD was attenuated but retained significance (β=0.29, 95% CI= 0.11 to 0.47).

In the full multivariable models, estrogen only <5y, estrogen+ progesterone <5 years, and estrogen + progesterone >5 years had significantly higher mean V measures than never users. The largest estimate was estrogen+ progesterone <5y (β=0.28, 95% CI= 0.13 to 0.43). With stratification for menopause type, natural menopause indicated significance for estrogen only >5y, estrogen + progesterone <5y, and estrogen + progesterone >5y, where estrogen only >5y was (β=0.50, 95% CI= 0.17 to 0.84). The full model stratification for PMD did not indicate differences in mean V75.

In the multivariable model + PMD, the mean V75 for estrogen + progesterone <5y was significantly greater than the reference (β=0.19, 95% CI= 0.05 to 0.33). Additionally, stratification for menopause type yielded significant estimates for natural menopause estrogen+ progesterone <5y (β=0.26, 95% CI= 0.10 to 0.42) and estrogen+ progesterone >5y (β=0.26, 95% CI= 0.08 to 0.44).

MHT: Secondary Analysis

In sensitivity analyses, we restricted to high resolution images (N=862), estimates were comparable. Exceptions included the age + BMI model stratification by menopause type; the mean V75 high resolution for past MHT users was greater than never users (β=0.35, 95% CI= 0.11 to 0.58). Additionally, the full model estimate for estrogen only >5y was greater than the reference (β=0.24, 95% CI= 0.06 to 0.41), and the full model stratification by menopause type gave a significant estimate for past MHT users (β=0.38, 95% CI= 0.13 to 0.63).

DISCUSSION

Results indicated that longer durations of MHT use were generally associated with higher V measures. Specifically, estrogen + progesterone >5y groups in both the age + BMI and the adjusted model exhibited significantly higher mean V measures; this effect persisted in sensitivity analyses. Notably, after adjusting for PMD, the effect of the estrogen + progesterone >5y groups was no longer significant, however the continued effect of the estrogen + progesterone <5y group suggests that compared to estrogen alone, estrogen + progesterone may have a greater impact on risk, as measured by V metric. Compared to PMD, the V metric may therefore be a more sensitive measure for evaluating tissue changes resulting from different forms and durations of MHT, as well as potentially subsequent risk of breast cancer.

The age + BMI model indicated that mean V75 estimates for estrogen only (<5y and >5y) and estrogen + progesterone (<5y and >5y) were greater than never users. For those with natural menopause in the age + BMI model, estrogen only >5y and estrogen + progesterone (<5y and >5y) retained significant estimates. When this model was adjusted for PMD, the estrogen + progesterone <5y participants with high PMD had a mean V75 estimate shown to be greater than never users. In the multivariable model, the mean V75 estimate for estrogen <5y and estrogen + progesterone (<5y and >5y) was greater than for never users. Among natural menopause users, estrogen only >5y and estrogen + progesterone (<5y and >5y) had significantly greater mean V75 measures.

The multivariable model adjusted for PMD yielded a greater V75 mean for estrogen + progesterone <5y compared to never users. Stratification by menopause gave significant estimates for natural menopause estrogen + progesterone (<5y and >5y). Secondary analyses resembled these results, however natural menopause in the age + BMI and multivariable model

gave significantly greater mean V75 (high resolution) estimates for past users, compared to never users. These findings support previous research that indicates MHT use in general is associated with higher quantities of dense tissue, as measured by PMD or V[1,10].

Additionally, our results show that different forms of MHT may have varying impacts. Estrogen + progesterone groups generally had higher mean V75 estimates than estrogen only, and also showed significant estimates in stratification for natural menopause and high PMD, while estrogen only did not. This aligns with findings that highlight the increased risk of breast cancer from estrogen + progesterone as compared to only estrogen[14]. The trend was present in secondary analyses for V75 high resolution as well.

Along with the kind of MHT, duration of treatment had an effect on V metric as well. In the main analysis, >5y categories were more consistently significant than <5y categories (for both estrogen only and estrogen + progesterone). This is exemplified in the age + BMI and multivariable models: Almost all estimates of estrogen >5y and estrogen + progesterone >5y are significantly higher than never users. This trend is also present in secondary analyses. This supports the notion that longer durations of MHT may increase physiological effects, including the V metric.

Results show that the trend between physiological factors (PMD, body composition, surgery) and the V metric continues to be evident. Considering that body physiology can be greatly affected by endocrines, these analyses support that MHT may have significant hormonal impact. After adjustment for PMD and BMI, there was a strong association between MHT users and higher mean V75 measures across models, compared to mean V75 in never users. The association was mitigated to an extent with the inclusion of relevant breast cancer risk factors in the multivariable model, but remained significant across multiple categories, and these covariates

further explain variance in the model. Stratification suggests that type of menopause may modify the effect, as women that indicated natural menopause consistently had larger estimates for mean V75 across all models, compared to surgical menopause.

PMD was also indicated to be associated with V: Age + BMI models across main and secondary analyses had significant estimates. However, several estimates in the multivariable model were marginally significant for high PMD, and the multivariable + PMD model yielded significant results as well. This, along with the measured correlation between PMD and V, supports previous findings that the two measures are associated. This offers more evidence that MHT influences both PMD and V measures.

CONCLUSIONS

The findings indicated that both estrogen and estrogen + progesterone menopausal hormone therapy use for either duration significantly increased V measures compared to those that had never used therapy. Specifically, estrogen + progesterone showed a stronger association; its effect remained after adjustment for percent mammogram density. Results showed that treatment durations of more than 5 years generally increased V measures more than treatment durations of 5 or less years, however this trend was not universal.

The study does have limitations. MHT status is self-reported and is therefore subject to error. Considering this, trends regarding MHT use that were found have been supported in previous literature, specifically that MHT use has decreased, but that estrogen only is still the most common approach[11]. MHT status was evaluated year to year and conflicting responses were omitted. Additionally, the majority of participants were white and generalization to other populations may be problematic.

However, there are notable strengths to this study. The automation of the texture measure V as well as the validity of PMD derived from mammograms both serve to reduce measurement error. Further, conducting analyses at higher resolution yielded similar results, which supports the reliability of these measures. Stratifying allowed for effect modification to be evaluated and effectively identified influential covariates, particularly the association of V independent of PMD. We also tested correlation between V and PMD to reinforce previous findings of association. Additionally, adjusting for multiple covariates allowed for more accurate estimations of variation as explained by our models.

The derived association between MHT status and the V measure is supported by findings that indicate associations between hormonal replacement therapy and mammographic density, which show a strong direct relationship, particularly with estrogen. As various texture features have been indicated as predictors of percent density, these results further suggest that while a correlation may be present between the two measures, the V metric's predictive ability remains independent from PMD.

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Table 1. Participant Characteristics

V75 Low	MHT Status						
	Never (N=702)	Past (N=334)	Estrogen <5y (N=176)	Estrogen >5y (N=351)	Est. & Progest. <5y (N=192)	Est. & Progest. >5y (N=148)	Other (N=83)
Age at mammogram, years	58.5 (7.7)	62.2 (7.8)	53.1 (6.8)	57.4 (7.8)	54.4 (5.3)	58.3 (7.0)	58.4 (7.5)
BMI at mammogram	26.7 (5.7)	25.9 (4.9)	26.7 (5.4)	26.0 (5.2)	25.0 (4.4)	25.0 (4.6)	25.4 (4.7)
Non-white, %	3.3	6.9	2.8	4.0	2.1	5.4	7.2
Type of menopause							
.	3.9	4.8	1.1	0.6	5.7	4.1	6.0
Natural	67.8	56.9	14.8	9.4	82.8	73.0	55.4
Surgical	28.4	38.3	84.1	90.0	11.5	22.0	38.6
Family history of breast cancer							
No	86.6	83.8	93.2	88.9	94.8	86.5	89.2
Yes	13.4	16.2	6.8	11.1	5.2	13.5	10.8
History of benign breast disease							
No	79.3	76.4	76.7	73.2	75.0	75.7	81.9
Yes	20.7	23.7	23.3	26.8	25.0	24.3	18.1
Age at menarche, years	12.4 (1.6)	12.5 (1.4)	12.3 (1.7)	12.5 (1.5)	12.3 (1.3)	12.7 (1.5)	12.7 (1.5)
Age at menopause, years	47.3 (6.6)	46.4 (6.6)	42.9 (7.2)	41.1 (6.6)	48.6 (4.8)	45.7 (6.9)	45.8 (7.0)
Parity							
Mean parity	3.4 (1.5)	3.2 (1.5)	2.9 (1.4)	2.9 (1.3)	2.9 (1.3)	2.8 (1.3)	3.1 (1.6)
nulliparous	8.3	7.8	11.4	10.3	11.5	12.8	9.6
1	5.0	7.8	10.2	11.4	12.5	11.5	7.2
2	26.2	23.7	30.1	28.8	25.0	29.7	33.3
3	24.4	29.3	25.6	26.5	26.0	21.6	20.5
4+	36.2	31.4	22.7	23.1	25.0	24.3	28.9
Total breastfeeding							
<1 month	38.2	36.2	34.7	41.3	32.8	33.1	39.8
1-6 months	20.5	27.5	22.7	21.1	24.0	19.6	16.9
7-12 months	11.7	9.3	7.4	9.4	13.5	11.5	13.3
>=13 months	22.1	20.4	25.0	18.8	19.3	23.0	21.7
.	7.6	6.6	10.2	9.4	10.4	12.8	8.4
Age at first birth, years	25.4 (3.4)	25.3 (3.4)	24.5 (3.2)	24.3 (3.3)	25.0 (3.7)	25.5 (3.8)	25.6 (3.4)
V75, low	-0.43 (0.95)	-0.30 (0.93)	-0.09 (0.90)	-0.22 (0.97)	0.07 (0.95)	-0.04 (0.96)	-0.24 (0.87)
V75, high	-0.52 (0.90)	-0.43 (0.95)	-0.29 (0.87)	-0.24 (1.00)	-0.08 (1.01)	-0.02 (0.76)	-0.21 (0.89)
Percent memmographic density	23.18 (17.93)	23.58 (16.93)	30.69 (18.18)	26.54 (16.54)	32.21 (18.63)	29.16 (17.32)	27.56 (18.29)

Table 2: Age + BMI Model, Multivariable Model

V75 Low

	Age + BMI					Age + BMI: Natural Menopause					Age + BMI: Surgical Menopause					Age + BMI: Low PMD					Age + BMI: High PMD				
MHT Status	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value
Never	0 (ref)	702				0 (ref)	476				0 (ref)	199				0 (ref)	415				0 (ref)	287			
Past	0.13	334	0.01	0.25	0.036	0.16	190	0.01	0.31	0.034	-0.11	128	-0.33	0.10	0.302	0.05	188	-0.07	0.18	0.919	0.10	146	-0.08	0.27	0.110
Estrogen <5y	**0.27**	**176**	**0.12**	**0.42**	**<.001**	0.26	36	-0.09	0.60	0.146	0.09	148	-0.11	0.28	0.368	0.24	66	0.04	0.44	0.348	0.09	110	-0.10	0.28	0.421
Estrogen >5y	**0.16**	**351**	**0.04**	**0.27**	**0.007**	**0.50**	**33**	**0.19**	**0.81**	**0.002**	-0.09	316	-0.26	0.08	0.287	0.03	158	-0.11	0.17	0.338	0.09	193	-0.06	0.24	0.016
Est + Prog <5y	**0.36**	**192**	**0.21**	**0.50**	**<.001**	**0.47**	**159**	**0.30**	**0.63**	**<.001**	-0.10	22	-0.50	0.31	0.634	0.22	70	0.02	0.41	0.793	**0.29**	**122**	**0.11**	**0.47**	**0.003**
Est + Prog >5y	**0.29**	**148**	**0.13**	**0.45**	**<.001**	**0.47**	**108**	**0.28**	**0.65**	**<.001**	-0.33	34	-0.66	0.01	0.054	0.20	63	0.00	0.40	0.023	0.19	85	-0.02	0.40	0.014
Other	0.11	83	-0.09	0.32	0.283	0.25	46	-0.02	0.51	0.071	-0.12	32	-0.47	0.22	0.484	-0.05	35	-0.31	0.20	0.983	0.04	48	-0.22	0.30	0.183
P-trend	**<0.01**					**<0.01**					**<0.01**					**<0.01**					**<0.01**				

	Full Model					Full: Natural Menopause					Full: Surgical Menopause					Full: Low PMD					Full: High PMD				
MHT Status	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value
Never	0 (ref)	702				0 (ref)	476				0 (ref)	199				0 (ref)	415				0 (ref)	287			
Past	0.11	334	-0.02	0.23	0.090	0.15	190	0.00	0.31	0.050	-0.15	128	-0.37	0.08	0.200	0.05	188	-0.08	0.18	0.478	0.07	146	-0.11	0.26	0.437
Estrogen <5y	**0.27**	**176**	**0.11**	**0.43**	**0.001**	0.34	36	-0.04	0.72	0.082	0.09	148	-0.11	0.29	0.387	0.25	66	0.05	0.46	0.016	0.07	110	-0.13	0.28	0.484
Estrogen >5y	0.15	351	0.03	0.27	0.018	**0.50**	**33**	**0.17**	**0.84**	**0.003**	-0.08	316	-0.26	0.09	0.348	0.01	158	-0.13	0.16	0.861	0.07	193	-0.09	0.24	0.383
Est + Prog <5y	**0.28**	**192**	**0.13**	**0.43**	**<.001**	**0.38**	**159**	**0.21**	**0.56**	**<.001**	-0.11	22	-0.51	0.29	0.603	0.19	70	-0.01	0.39	0.060	0.19	122	0.00	0.39	0.050
Est + Prog >5y	**0.23**	**148**	**0.06**	**0.40**	**0.007**	**0.41**	**108**	**0.22**	**0.61**	**<.001**	-0.36	34	-0.72	0.00	0.047	0.12	63	-0.09	0.33	0.254	0.15	85	-0.07	0.38	0.178
Other	0.10	83	-0.11	0.31	0.367	0.21	46	-0.06	0.48	0.127	-0.10	32	-0.48	0.27	0.589	-0.05	35	-0.32	0.22	0.706	-0.01	48	-0.29	0.26	0.917
P-trend	**<0.01**					**<0.01**					**<0.01**					**<0.01**					**<0.01**				

	Full Model + PMD					Full + PMD: Natural Menopause					Full + PMD: Surgical Menopause				
MHT Status	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value
Never	0 (ref)	702				0 (ref)	476				0 (ref)	199			
Past	0.06	334	-0.05	0.17	0.281	0.10	190	-0.04	0.24	0.171	-0.13	128	-0.32	0.07	0.199
Estrogen <5y	0.15	176	0.01	0.29	0.036	0.22	36	-0.13	0.56	0.218	0.03	148	-0.15	0.20	0.777
Estrogen >5y	0.05	351	-0.06	0.16	0.402	0.37	33	0.07	0.67	0.017	-0.11	316	-0.26	0.04	0.166
Est + Prog <5y	**0.19**	**192**	**0.05**	**0.33**	**0.007**	**0.26**	**159**	**0.10**	**0.42**	**0.002**	-0.15	22	-0.51	0.20	0.392
Est + Prog >5y	0.14	148	-0.01	0.29	0.074	**0.26**	**108**	**0.08**	**0.44**	**0.004**	-0.33	34	-0.64	-0.01	0.043
Other	-0.03	83	-0.22	0.16	0.771	0.05	46	-0.19	0.30	0.679	-0.22	32	-0.55	0.12	0.201
P-trend	**<0.01**					**<0.01**					**<0.01**				

Supplementary Table 1. Participant Characteristics, V75 High Resolution

V75 High	MHT Status						
	Never (N=247)	Past (N=119)	Estrogen <5y (N=90)	Estrogen >5y (N=194)	Est. & Progest. <5y (N=98)	Est. & Progest. >5y (N=76)	Other (N=38)
Age at mammogram, years	56.4 (8.5)	62.0 (9.1)	51.3 (6.9)	55.6 (8.4)	53.6 (5.7)	56.6 (7.9)	54.9 (6.3)
BMI at mammogram	25.7 (4.9)	25.2 (5.1)	26.2 (5.0)	24.9 (4.5)	24.6 (4.0)	24.4 (4.7)	24.4 (3.8)
Non-white, %	2.4	8.4	2.2	3.6	2.0	6.6	2.6
Type of menopause							
.	2.4	4.2	.	0.52	2.0	6.6	5.3
Natural	58.8	68.9	5.6	6.7	88.8	72.4	57.9
Surgical	38.9	26.9	94.4	92.8	9.2	21.1	36.8
Family history of breast cancer							
No	87	82.4	91.1	91.2	96.9	88.2	89.5
Yes	13	17.6	8.9	8.8	3.1	11.8	10.5
History of benign breast disease							
No	74.9	76.5	77.8	71.3	72.5	76.3	73.7
Yes	25.1	23.5	22.2	28.9	27.6	23.68	26.3
Age at menarche, years	12.2 (1.7)	12.6 (1.4)	12.4 (1.5)	12.7 (1.3)	12.4 (1.3)	13.0 (1.5)	12.4 (1.3)
Age at menopause, years	45.9 (7.4)	46.7 (6.8)	42.0 (7.1)	40.4 (6.5)	48.2 (4.5)	43.9 (7.4)	44.4 (7.8)
Parity							
Mean parity	3.1 (1.5)	3.1 (1.5)	2.5 (1.3)	2.7 (1.3)	2.7 (1.3)	2.7 (1.4)	3.0 (1.7)
nulliparous	11.3	10.9	12.2	9.8	14.3	17.1	13.2
1	7.3	8.4	14.4	12.9	14.3	14.5	13.2
2	28.3	26.9	37.8	31.4	24.5	30.3	29.0
3	26.7	26.9	23.3	27.3	28.6	19.7	13.2
4+	26.3	26.9	12.2	18.6	18.4	18.4	31.6
Total breastfeeding							
<1 month	31.6	35.3	30.0	37.6	28.6	34.2	31.6
1-6 months	20.2	26.1	25.6	19.1	25.5	9.2	15.8
7-12 months	13	9.2	6.7	11.3	13.3	10.5	10.5
>=13 months	23.9	21	27.8	22.7	20.4	29.0	31.6
.	11.3	8.4	10.0	9.3	12.2	17.1	10.5
Age at first birth, years	25.2 (3.2)	25.1 (3.0)	24.2 (3.0)	24.1 (3.7)	25.4 (4.1)	25.4 (4.1)	25.0 (2.9)
V75, high	-0.52 (0.90)	-0.43 (0.95)	-0.29 (0.87)	-0.24 (1.00)	-0.08 (1.01)	-0.02 (0.76)	-0.21 (0.89)
Percent memmographic density	27.12 (17.02)	24.49 (13.89)	32.03 (17.53)	29.79 (15.55)	32.65 (16.52)	31.53 (15.83)	31.02 (17.19)

Supplementary Table 2: Sensitivity Analyses for Age + BMI Model, Multivariable Model

V75 High

	Age + BMI v75 high					Age + BMI: Natural Menopause					Age + BMI: Surgical Menopause					Age + BMI v75 high: Low PMD					Age + BMI v75 high: High PMD				
MHT Status	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value
Never	0 (ref)	247				0 (ref)	476				0 (ref)	199				0 (ref)	415				0 (ref)	287			
Past	0.17	119	-0.03	0.37	0.097	**0.35**	**190**	**0.11**	**0.58**	**0.004**	-0.26	128	-0.64	0.12	0.185	-0.01	188	-0.24	0.22	0.919	0.22	146	-0.05	0.49	0.110
Estrogen <5y	0.17	90	-0.05	0.39	0.128	-0.12	36	-0.89	0.65	0.766	-0.01	148	-0.28	0.25	0.914	0.14	66	-0.15	0.43	0.348	0.11	110	-0.15	0.37	0.421
Estrogen >5y	**0.22**	**194**	**0.05**	**0.39**	**0.010**	**0.64**	**33**	**0.15**	**1.13**	**0.010**	-0.02	316	-0.25	0.21	0.879	-0.11	158	-0.33	0.11	0.338	0.26	193	0.05	0.46	0.016
Est + Prog <5y	**0.33**	**98**	**0.12**	**0.54**	**0.002**	**0.52**	**159**	**0.28**	**0.76**	**<.001**	-0.24	22	-0.85	0.38	0.454	0.04	70	-0.25	0.33	0.793	**0.37**	**122**	**0.12**	**0.62**	**0.003**
Est + Prog >5y	**0.43**	**76**	**0.20**	**0.66**	**<.001**	**0.62**	**108**	**0.35**	**0.89**	**<.001**	0.03	34	-0.45	0.51	0.917	0.35	63	0.05	0.66	0.023	0.34	85	0.07	0.62	0.014
Other	0.21	38	-0.10	0.51	0.180	0.40	46	0.01	0.78	0.046	-0.07	32	-0.58	0.44	0.796	0.00	35	-0.42	0.41	0.983	0.24	48	-0.12	0.60	0.183
P-trend	**<0.01**					**<0.01**					**<0.01**					**<0.01**					**<0.01***				

	Full Model v75 high					Full Model: Natural Menopause					Full Model: Surgical Menopause					Full Model v75 high: Low PMD					Full Model v75 high: High PMD				
MHT Status	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value
Never	0 (ref)	247				0 (ref)	476				0 (ref)	199				0 (ref)	415				0 (ref)	287			
Past	0.19	119	-0.02	0.40	0.078	**0.38**	**190**	**0.13**	**0.63**	**0.003**	-0.34	128	-0.75	0.08	0.112	0.00	188	-0.23	0.24	0.983	0.28	146	-0.02	0.59	0.066
Estrogen <5y	0.19	90	-0.04	0.42	0.101	-0.20	36	-1.04	0.65	0.650	0.00	148	-0.28	0.28	0.990	0.20	66	-0.10	0.51	0.183	0.05	110	-0.23	0.34	0.715
Estrogen >5y	**0.24**	**194**	**0.06**	**0.41**	**0.009**	0.38	33	-0.14	0.91	0.150	0.01	316	-0.24	0.26	0.918	-0.06	158	-0.29	0.17	0.613	0.22	193	-0.01	0.45	0.056
Est + Prog <5y	0.22	98	0.00	0.44	0.049	**0.40**	**159**	**0.15**	**0.66**	**0.002**	-0.11	22	-0.72	0.50	0.714	0.06	70	-0.24	0.36	0.690	0.21	122	-0.06	0.49	0.122
Est + Prog >5y	**0.38**	**76**	**0.13**	**0.63**	**0.003**	**0.55**	**108**	**0.26**	**0.83**	**<.001**	-0.01	34	-0.56	0.53	0.959	0.32	63	-0.01	0.64	0.057	0.26	85	-0.05	0.57	0.096
Other	0.13	38	-0.19	0.45	0.416	0.30	46	-0.10	0.70	0.137	-0.20	32	-0.76	0.36	0.480	0.00	35	-0.41	0.41	1.000	0.13	48	-0.27	0.53	0.520
P-trend	**<0.01**					**<0.01**					**<0.01**					**<0.01**					**<0.01**				

	Full Model + PMD					Full + PMD: Natural Menopause					Full + PMD: Surgical Menopause				
MHT Status	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value	Estimate	N	95% CI		P-value
Never	0 (ref)	247				0 (ref)	476				0 (ref)	199			
Past	0.09	119	-0.09	0.28	0.324	0.25	190	0.02	0.48	0.034	-0.32	128	-0.68	0.03	0.073
Estrogen <5y	0.10	90	-0.10	0.31	0.315	-0.03	36	-0.81	0.75	0.938	-0.07	148	-0.31	0.17	0.574
Estrogen >5y	0.09	194	-0.07	0.24	0.292	0.21	33	-0.28	0.69	0.396	-0.11	316	-0.33	0.10	0.293
Est + Prog <5y	0.12	98	-0.08	0.32	0.240	0.25	159	0.02	0.49	0.036	0.00	22	-0.52	0.52	0.992
Est + Prog >5y	0.24	76	0.02	0.46	0.034	**0.37**	**108**	**0.11**	**0.64**	**0.006**	-0.16	34	-0.63	0.31	0.503
Other	0.04	38	-0.24	0.33	0.762	0.13	46	-0.24	0.50	0.500	-0.22	32	-0.70	0.26	0.358
P-trend	**<0.01**					**<0.01**					**<0.01**				