A Longitudinal Study of the Effects of Menopause on Mammographic Features[1]

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Abstract

Menopause has an important influence on risk of breast cancer. We have examined longitudinally the effect of menopause on mammographic densities, a strong risk factor for the disease, in women in the Canadian National Breast Screening Study. Baseline mammograms from women in the National Breast Screening Study, who were premenopausal at entry and had undergone menopause after entry, were compared with the mammogram that most closely followed menopause, using a computer-assisted method of measurement. The changes seen in the mammograms of these subjects were compared with those in an age-matched group of women who were also premenopausal at entry, had been followed for the same length of time, and had not experienced menopause. The results of this longitudinal study show that menopause has effects on characteristics of the mammogram that, over the same period of time, are greater than the effects of age. These effects are a reduction in the area of radiologically dense tissue, an increase in the area of nondense tissue, and a decrease in the percentage of density. However, these changes do not fully account for the effects of age on mammographic densities seen in cross-sectional data. Menopause is associated with distinct changes in the mammogram that account for some, but not all, of the observed association of increasing age with decreasing percentage of mammographic density. The observed changes in the morphology of the breast may explain some of the effect that menopause has on breast cancer risk.

Introduction

The purpose of this study is to examine the influence of menopause on mammographic densities. Menopause appears to have profound importance in the etiology of breast cancer and is associated with a striking change in the slope of the age-specific incidence (log-log) curve for breast cancer (1). Age at menopause is known to influence risk of the disease (2), and the large differences in rates of breast cancer that exist between countries are most marked after the age at which menopause usually occurs (3).

Mammographic densities reflect the tissue composition of the breast (4). Radiologically dense tissue in the breast indicates stroma and epithelium, whereas lucent tissue indicates fat. Changes in the tissue composition of the breast occur with increasing age, and the amounts of stroma and epithelium decrease, whereas the amount of fat increases. These changes are reflected in a decrease in the prevalence of mammographic densities with increasing age and are illustrated in Fig. 1. The figure shows the average percentage of density in women in the Canadian NBSS[3] according to age. The data shown are for control subjects in a previously published nested case-control study of mammographic densities and breast cancer risk in the NBSS (5). At ages 40–44 years, mean percentage of density is 38%, whereas at ages 55–59 years, it is 18%, a 20% difference. Menopause is thought to be a more important influence than age on the decline in mammographic densities (6). However, this view is based entirely on cross-sectional data in which the mammographic features of different women are compared, rather than on observation of longitudinal change in the radiological characteristics of the breast in individuals.

In the present study, we have examined longitudinally the effect of menopause on mammographic densities by exploiting the availability of serial mammograms in subjects obtained over several years within the NBSS (7, 8), a randomized controlled trial of screening for breast cancer. We have compared the changes occurring in women who experienced menopause with those in an age-matched group who remained premenopausal during the same interval.

Materials and Methods

General Method. The general method used was to identify women within the Canadian NBSS, a multicenter randomized controlled trial of screening for breast cancer, who had been allocated to the mammography arm of the study, in which they received annual mammography for 5 years. We selected subjects who were premenopausal at entry and had undergone menopause after entry. We compared the mammogram obtained at entry with the mammogram that most closely followed menopause, as well as the mammogram taken 5 years after entry, using a computer-assisted method of measurement. The changes seen in the mammograms of these subjects were compared with those in an age-matched group of women who were

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[3] The abbreviations used are: NBSS, National Breast Screening Study; HRT, hormone replacement therapy.

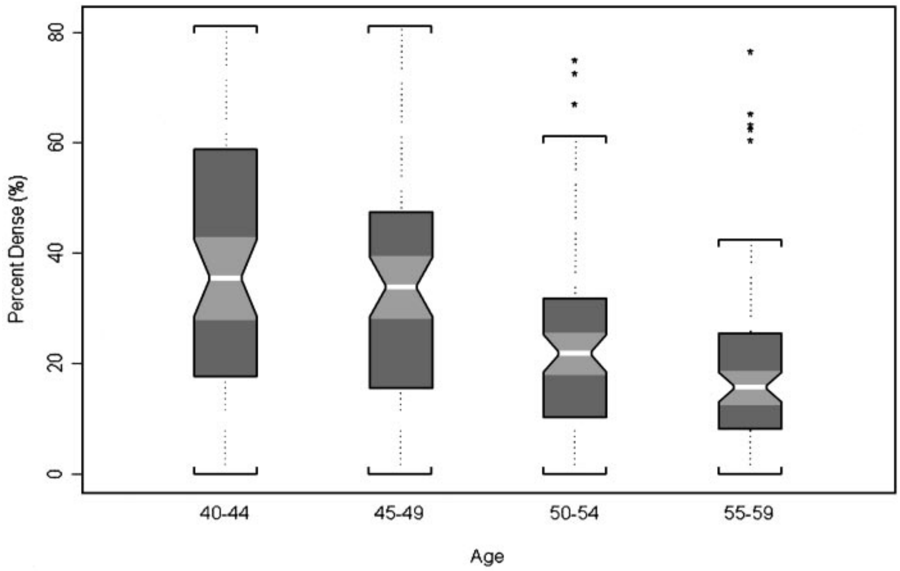

Fig. 1. Distributions of percentage of density by age for NBSS control women.

also premenopausal at entry, had been followed for the same length of time, and had not experienced menopause.

Selection of Subjects. Women who participated in the NBSS annually completed a self-administered questionnaire that asked about several variables including demographic information, hormone use, body weight (at baseline only), and menstrual periods. We selected two cohorts of women who had been screened annually for 5 years in the NBSS. We selected one group of women who were premenopausal at entry to the NBSS and became postmenopausal (defined below) at a subsequent screening examination. These subjects are referred as the **pre-postmenopausal group**. A second group of women, who remained premenopausal, were selected as a comparison group and individually matched to the subjects in the pre-postmenopausal group. We refer to these subjects as the **premenopausal group**. The matching characteristics were age at entry to the NBSS (within 1 year), mammography center, and year of entry to the NBSS.

Menopausal status was defined by the subjects' response to a question asked annually ("Are you still having menstrual periods?"). All subjects potentially eligible for the present study had answered "yes" to this question at entry to the NBSS. Those who responded "no" to this question on two consecutive subsequent annual visits were classified as postmenopausal from the time of the first of these responses. These subjects comprised the pre-postmenopausal group of this study. The application of this definition meant that the latest that a subject could have menopause and be included in the pre-postmenopausal group was between 3 and 4 years after entry, and the earliest was between entry and the first annual visit. The individually matched comparison group of premenopausal women had answered "yes" to this question at all visits, up to and including the visit at which their corresponding matched subject had been classified as postmenopausal.

Women who had had a hysterectomy or an oophorectomy were excluded from both groups, as were women who were using HRT at the time of either the baseline or postmenopause screening visit. Previous hormone use was accepted, but use was ascertained only once per year, and time since last use was not determined.

Measurement of Mammograms. Mammograms from baseline and from the screening examination after the cessation of menstrual periods and the corresponding mammograms for the matched control were analyzed using a computer-assisted method (9–11). In this method, images were digitized and presented to the observer. We digitized images using a Lumisys model 85, which provides up to 12-bit density resolution and 50 μm spatial resolution. One pixel was 0.0676 mm^2. An observer made the classification, using a computer to provide interactive feedback about the optical density information of the image. Images from subjects in the premenopausal and pre-postmenopausal groups were randomly ordered, and furthermore, the pairs of baseline and post-baseline films were also randomly ordered. The images were thus measured without knowledge of group membership or of the sequence in which the images had been taken.

The observer selected a threshold gray value to separate the image of the breast from the background and selected a second threshold to identify the edges of region(s) that were representative of radiographically dense tissue. We then calculated the histogram of pixel values within these boundaries. Summation over the appropriate regions of the histogram allowed calculation of the size of the projected area of the breast in the image and of the area of density. The percentage of radiographic density is the area of dense tissue divided by the entire projected area of the breast and multiplied by 100. The system automatically recorded thresholds that are set for segmentation of the image. The area of nondense tissue was calculated by subtracting the dense area from the total area.

Reliability was assessed by rereading a randomly selected 10% of images, randomly distributed throughout each read, and was consistently >0.9.

Statistical Methods. Paired *t* tests were used to compare continuous baseline demographic variables and mammographic measures in the pre-postmenopausal and premenopausal groups. McNemar's test was used to compare categorical variables.

The relationship between menopause and the change in mammographic measures over time, in which we compared premenopausal women with pre-postmenopausal women, was

Table 1 Selected baseline demographic characteristics of subjects

		N	Pre-postmenopausal	Premenopausal	P^a
Risk factors	Age (yrs)	202	46.5 (3.3)	46.5 (3.3)	1.00
	Pregnant ever (%)	202	88.1	87.1	0.76
	No. of live births	202	3.0 (7.0)	2.5 (1.9)	0.35
	Age at first birth (yrs) (parous only)	178, 176	23.7 (5.6)	23.5 (7.1)	0.69^b
	Age at menarche (yrs)	202	12.8 (1.4)	12.9 (1.9)	0.48
	Weight (kg)	202	65.2 (11.7)	65.2 (12.7)	0.98
	Height (cm)	201, 202	163.1 (6.2)	162.5 (5.5)	0.31
Hormones	Oral contraceptive use status (% yes)	202	61.9	63.4	0.76
	Length of oral contraceptive use (months) (users only)	125, 128	59.6 (51.8)	60.0 (46.3)	0.96^c
	Length of oral contraceptive use (months) (all pairs)	202	36.9 (50.0)	38.0 (46.8)	0.75^d
	HRT use status (% yes)	202	7.4	4.5	0.22
	Duration of HRT use (months) (users only)	15, 9	12.0 (20.8)	15.4 (29.4)	0.74^c
	Duration of HRT use (months) (all pairs)	202	0.9 (6.3)	0.69 (6.7)	0.76^d
Smoking	Smoking status (% yes)	202	45.5	48.5	0.53
	Smoking amount (cigarettes/day) (smokers only)	92, 98	16.4 (11.7)	14.3 (11.8)	0.23^c
	Smoking amount (cigarettes/day) (all pairs)	202	7.5 (11.3)	7.0 (10.9)	0.64^d
	Duration of smoking (yrs) (smokers only)	92, 98	17.9 (10.4)	14.9 (9.4)	0.04^c
	Duration of smoking (yrs) (all pairs)	202	8.2 (11.3)	7.2 (9.9)	0.35^d
	Pack-years of smoking (smokers only)	92, 98	358.6 (339.6)	271.7 (321.9)	0.07^c
	Pack-years of smoking (all pairs)	202	163.5 (290.2)	131.8 (261.8)	0.25^d
Mammographic Features	Percent dense (%)	202	31.6 (20.6)	36.5 (21.9)	0.02
	Dense area (cm^2)	202	32.0 (22.4)	37.0 (23.9)	0.03
	Non-Dense Area (cm^2)	202	81.4 (48.1)	78.0 (55.4)	0.53
	Total Area (cm^2)	202	113.4 (46.0)	115.0 (51.5)	0.73

[a] *P*s are based on a paired *t* test for continuous variables and McNemar's test for categorical variables.
[b] *P* is based on a paired *t* test of all 202 pairs where nulliparous women are coded as 0, whereas the mean age at first birth is subtracted from the parous women. The means shown in the table have been calculated for parous women only.
[c] *P* is based on a two sample (unpaired) *t* test of applicable observations (*e.g.*, smokers only).
[d] *P* is based on a paired *t* test of all 202 pairs where nonapplicable observations are coded as 0 (*e.g.*, those who do not smoke are coded as 0 when comparing smoking amount).

examined using regression models. The response variable in these models was the paired difference between the premenopausal and pre-postmenopausal women in the change in the mammographic measure over time. The effect of change in menopausal status on change in mammographic characteristics was assessed after controlling for other baseline variables using regression analysis. The baseline variables whose influence was examined were age at menarche, age at first birth, parity, number of births, previous use of oral contraceptives, smoking status, years of smoking, height, and weight.

Results

Characteristics of Subjects. Table 1 shows selected baseline characteristics of subjects who experienced menopause and the comparison group who remained premenopausal. The age-matched subjects in the two groups were, on average, 46.5 years of age. None of the demographic, reproductive, or anthropometric variables examined differed significantly at the 5% level between matched pairs of subjects. Whereas there is no significant difference in the percentage of premenopausal and pre-postmenopausal women who smoked (45.5% *versus* 48.5%, respectively), ignoring the matching, the average number of years of smoking was significantly higher among pre-postmenopausal women (17.9 years *versus* 14.9 years; $P = 0.04$). Pack-years of smoking was associated with group at a borderline level of significance ($P = 0.07$) only among smokers, and in the matched pair analysis of all subjects, it shows no association with menopausal group ($P = 0.35$).

Although of the same age and menopausal status, women who were in the pre-postmenopausal group had a significantly lower percentage of density at baseline and a smaller area of dense breast tissue than women in the premenopausal group.

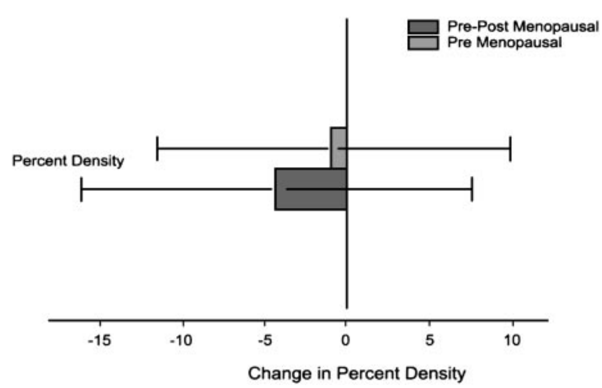

Fig. 2. Mean and SD of change in percentage of density.

The area of nondense tissue and total breast area were similar in the two groups.

Change in Mammographic Features: Unadjusted Analysis. Figs. 2 and 3 show the results of comparing mammograms from the pre-postmenopausal and premenopausal groups. Within each group, we compared the mammogram taken at baseline with the mammogram taken at the annual visit at which pre-postmenopausal subjects were classified as postmenopausal and the corresponding annual visit in each matched premenopausal subject. Between each group, we compared the difference in the mammographic measures of total area, dense area, nondense area, and percentage of density in these two mammograms.

As shown in Fig. 2, percentage of density decreased 5% in

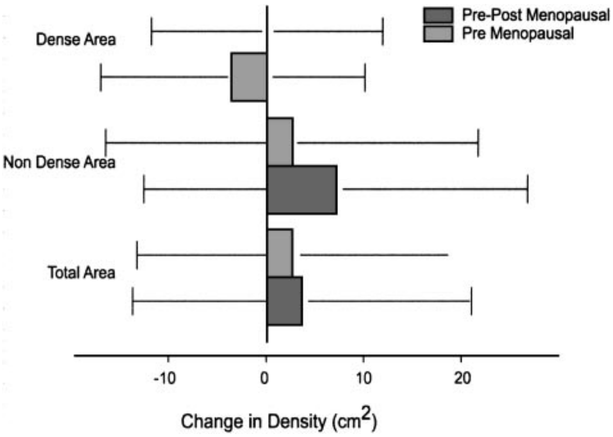

Fig. 3. Mean and SD of changes for each mammographic measure.

Table 2 Comparison of differences in change of mammographic measures between premenopausal and pre-postmenopausal subjects: results of multiple regression analysis

Mammographic measure	Unadjusted estimate	P^a	Adjusted estimate[b]	P^a
Percent dense (%)	−3.26	0.004	−3.05	0.01
Dense area (cm^2)	−3.39	0.007	−3.31	0.01
Nondense area (cm^2)	4.37	0.01	4.15	0.02
Total area (cm^2)	0.97	0.44	0.84	0.55

[a] *P*s are based on a paired *t* test of all 202 pairs.
[b] Adjustment for age at menarche, age at first birth, parity, number of births, previous use and duration of oral contraceptives, smoking status and duration, height, and weight.

the pre-postmenopausal group. Results of linear regression, given in Table 2, showed that compared with women who remained premenopausal, percentage of density decreased to a significantly greater extent in women who became postmenopausal (difference in change = −3.26 percentage points, P = 0.004). The area of dense breast tissue significantly decreased among pre-postmenopausal subjects compared with matched premenopausal comparison subjects (difference in change = −3.39 cms^2; P = 0.007), and conversely, the area of nondense tissue increased significantly (difference in change = 4.37 cms^2; P = 0.01). There was no statistically significant difference between the two groups in the change in total breast area (difference in change = 0.97 cms^2; P = 0.44). The changes in these measures in each group are shown in Fig. 3.

Change in percentage of density, dense area, and nondense area over time remained significantly different for premenopausal as compared with pre-postmenopausal women after controlling for these variables in a regression model.

Longer-Term Changes in Mammographic Features. The average interval between the mammogram taken at baseline, when all subjects were still menstruating, and the first postmenopausal mammogram was 1.5 years (SD = 0.6 years). The minimum interval was 0.8 years, and the maximum interval was 4.1 years. To estimate the longer-term effects of menopause on change in mammographic features, we compared the baseline mammogram in pre-postmenopausal subjects with the mammogram taken 5 years after entry to the NBSS, which was the last screening examination in this trial. Percentage of density decreased an average of 8 percentage points over this interval. The dense area decreased by an average of 6.8 cm^2, and the nondense area increased an average of 20.2 cm^2. In the premenopausal group, over the same period of time, percentage of density was reduced by 7%, dense area was reduced by an average of 3.8 cm^2, and nondense area was increased by an average of 14 cm^2.

Discussion

The results of this longitudinal study show that menopause has effects on characteristics of the mammogram that, over the same period of time, are greater than the effects of age. These effects are a reduction in percentage of density due to both a reduction in the area of radiologically dense tissue and an increase in the area of nondense tissue. Stromal and epithelial tissues are associated with radiological densities, and fat is associated with the nondense tissue in the mammogram, and the observed radiological changes associated with menopause thus indicate changes in the amounts of these tissues in the breast.

We are able to distinguish the effect of menopause on mammographic characteristics from the effects of age because we matched subjects closely on age when they entered the NBSS and their baseline mammogram was taken. Furthermore, we defined menopause as a report of no menstrual periods in two consecutive annual visits. We also limited the present study to women who experienced a spontaneous menopause and excluded women taking HRT (12). Our results are thus not influenced by HRT, which may increase mammographic densities (13). There is some evidence, based on a qualitative classification of mammographic appearances, that the time in the menstrual cycle may influence mammographic densities (14). Time in the menstrual cycle was not recorded for the subjects whose mammograms are assessed here, and variations in mammographic features due to the menstrual cycle might obscure change, particularly in members of the premenopausal group, who were menstruating at both mammographic examinations. However, the coefficients of variation for percentage of density and dense area in the second mammogram were respectively 64% and 67% for the premenopausal group and 68% and 72% for the pre-postmenopausal group. Thus, after allowing for differences in mean values, there was no evidence of greater variability in the mammogram in subjects who were still having menses. Furthermore, as we show here, the effect of the cessation of ovarian function on mammographic features is relatively small, and it is unlikely that fluctuations in ovarian function during the menstrual cycle have a major effect.

Because the screening program from which subjects were selected lasted only 5 years, and because our selection procedure for pre-postmenopausal subjects required two consecutive annual visits without menstrual periods, we selected, of necessity, women with a relatively early menopause. The median age at baseline of the pre-postmenopausal group in this study was 46 years, the average interval between baseline and the first postmenopausal mammogram was 1.5 years, and the median age at menopause was 47.5 years. The median age of menopause in white women from industrialized countries is 51 years (15).

Previous cross-sectional studies have shown that mammographic densities are influenced by age and menopausal status (6, 16, 17). Although distinct, the effects observed in this longitudinal study of the effects of menopause on mammographic densities do not fully account for the effects of age on mammographic densities seen in cross-sectional analysis. As shown in Fig. 1, the average percentage of density in women in the NBSS (5) differed by 20% between those ages 40–44 and

55–59 years, compared with the 8% reduction in percentage of density observed in the present study over 5 years in subjects who went through menopause, compared with 2% in women of the same age who did not experience menopause. These effects of age shown in Fig. 1 are present after taking into account baseline variables such as age at menarche, parity, and weight that may differ among women of different ages and give rise to differences in cross-sectional analysis (data not shown). Thus, changes in breast tissue as seen on the mammogram associated with aging itself, in addition to those associated with menopause, appear to be responsible in part for the reduction of percentage of density observed with increasing age. From the change observed here in subjects who have not experienced menopause, we estimate an average annual reduction in percentage of density of about 1%. Over a period of 15 years, changes of this magnitude, combined with the effects of menopause, could account for difference in percentage of density of about 20% seen in cross-sectional data between women ages 40–44 years and those ages 55–59 years.

Evidence of changes in mammographic characteristics preceding the last menstrual period is provided by the finding in the present study that there were differences in baseline mammographic characteristics in mammograms obtained when all subjects were of the same age and were still premenopausal. Years of smoking, which has previously been associated with menopause (18), was the only other variable found to differ in frequency between premenopausal and pre-postmenopausal groups. Age-related changes in levels of hormones preceding menopause may be responsible for the observed differences in baseline mammographic characteristics. Blood levels of both insulin-like growth factor I and prolactin decline with increasing age, and both have been found to be associated with mammographic density (19–24). There is also evidence that insulin-like growth factor I levels in breast tissue are associated with mammographic densities (25). Longitudinal studies that have examined hormonal changes preceding menopause have shown an increasing frequency of inadequate luteal function and anovulation and increasing variability in blood levels of estradiol, with maintenance of the average estradiol level until shortly before the last menstrual period. Blood levels of progesterone decline progressively over 4 years before the last menstrual period (22).

The decline in the prevalence of mammographically dense breast tissue in the population that occurs with increasing age (6, 26, 27) resembles the model of breast cancer incidence proposed by Pike *et al.* (1), based on the concept that the rate of "breast tissue ageing," which is closely associated with exposure of breast tissue to hormones, and the effects of hormones on the kinetics of breast cells, rather than chronological age, is the relevant measure for describing the incidence of breast cancer. The model includes age at menarche, age at first pregnancy, and age at menopause and has since been extended to incorporate the number and timing of pregnancies (28). After fitting numerical values for these parameters, Pike showed that cumulative exposure to "breast tissue ageing" provided a good fit to the actual age-specific incidence curve for breast cancer.

There are several similarities between the factors that influence mammographic densities and Pike's concept of "breast tissue ageing." The influence of menopause on mammographic densities is shown in the present study, and the effect of pregnancy in reducing mammographic density has been described by several authors (6, 16, 29). Cumulative exposure to mammographic densities may thus reflect cumulative exposure to hormones that stimulate cell division in the breast and may be an important determinant of breast cancer incidence. Therefore, we expect that events that increase or decrease cumulative exposure to mammographic densities will have corresponding effects on the incidence of the disease. Thus, late menarche, early first pregnancy, multiple pregnancies, and early menopause, which are all known to decrease risk of breast cancer, also decrease cumulative exposure to mammographic densities (2, 6, 16, 17). Conversely, early menarche, late age at first pregnancy, nulliparity, and late menopause increase cumulative exposure to dense tissue. By considering cumulative exposure to mammographically dense tissue in the population, given by the area under the curve of age-specific average densities, we may be able to account for key features of the age-specific incidence curve for breast cancer. Thus, the steeper premenopausal component of the age-incidence curve is associated with a higher prevalence of mammographic densities, and the less steep postmenopausal component is associated with a lower prevalence of densities and, as shown here, there is a reduction in mammographic densities at menopause, the event thought to be responsible the inflection in the age-specific incidence curve.

It is known that an early menopause reduces the risk of breast cancer (30). The reduction in breast density associated with menopause suggests that a reduction in the number of epithelial and stromal elements in the breast, occurring in response to changes in hormonal exposure, may be a key component of this effect. Further research is needed to identify the relationship between changes in mammographic density and changes in risk of breast cancer.

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