Reproductive and menstrual factors in relation to mammographic parenchymal patterns among perimenopausal women

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Summary The relationship between mammographic patterns and reproductive and menstrual factors was examined in 3640 Norwegian women, aged 40–56 years, participating in the Third Tromsø study conducted in 1986–87. Epidemiological data were obtained from questionnaires. The mammograms were categorised into five groups. This categorisation is based on anatomic–mammographic correlations, following three-dimensional (thick slice technique) histopathologic–mammographic comparisons, rather than simple pattern reading. Patterns 1–3 were combined into a low-risk group and patterns 4 and 5 into a high-risk group for analysis. Women who had more than four children were 90% less likely to have a high-risk pattern than nulliparous women (OR = 0.09, 95% CI 0.04–0.16) controlling for age, weight, height and menopausal status. Furthermore, those who first gave birth over 34 years of age were more than twice as likely to have a high-risk pattern than those giving birth in their teens (OR = 2.37, 95% CI 1.23–4.50) adjusting for parity. Among post-menopausal women, age at menarche was negatively (P for trend = 0.015) and late age at menopause positively (P for trend = 0.072) related to high-risk patterns. Among premenopausal women, age at menarche was positively related to high-risk patterns (P for trend = 0.001). Also, menopausal status rather than age was associated with high-risk patterns. These findings support the opinion that reproductive and menstrual factors are involved in determining the mammographic parenchymal pattern among perimenopausal women.

Keywords: mammography; Norway; parenchymal breast patterns; parity; reproductive factors; menarche; menopause; risk factors

There is now a large amount of evidence showing that mammographic parenchymal patterns are a marker of breast cancer risk (Saftlas and Sziko, 1987; Goodwin and Boyd, 1988; Brisson et al., 1989; Warner et al., 1992; Holowaty et al., 1993; Oza and Boyd, 1993).

The relationship between these mammographic features and risk factors for breast cancer has also been investigated. A consistent inverse association between high-risk parenchymal pattern and age, weight and parity has been reported. However, data regarding an association between these patterns and age at menarche, age at menopause and age at first birth are inconclusive (Bergkvist et al., 1987; Saftlas and Sziko, 1987; De Stavola et al., 1990; Oza and Boyd, 1993).

The aetiological mechanisms by which mammographic parenchymal pattern is associated with the occurrence of breast cancer are unknown. The purpose of this study was to examine whether reproductive and menstrual factors are involved in determining the mammographic parenchymal pattern among perimenopausal women in a population-based study.

Materials and methods

Mammographic screening was a part of the Third Tromsø study, a health survey of men and women living in Tromsø, Norway, in 1986 and 1987. Women born between 1930 and 1966 were invited to participate. Those aged 40 or older (n = 4323) were offered free mammography, with 3633 (85%) accepting. Details of the screening and case finding procedures are given elsewhere (Gram et al., 1989, 1990).

The participants in the Third Tromsø survey completed one questionnaire at the screening facility and another at home. The first questionnaire concerned disease history and aspects of living habits. The screeners also had their height and weight measured. The second questionnaire elicited information on reproductive variables, dietary habits, breast diseases and social and psychological conditions. The participants were asked to return this questionnaire by mail.

All screening mammograms, excluding those which detected breast cancer, were classified according to a system developed by one of the authors (LT). No details other than the date of birth were known to him. The Tabar system, patterns 1–5, is a further development of the mammographic parenchymal pattern classification. This classification is based on anatomic–mammographic correlations following three-dimensional (thick slice technique) histopathologic–mammographic comparisons rather than simple pattern reading as in the Wolfe system (Wolfe, 1976). Four out of the five patterns in the Tabar system may directly be compared to the patterns in the Wolfe system, i.e. low-risk patterns 2 and 3 equate to N1 and P1 respectively, and high-risk patterns 4 and 5 are equivalent to P2 and DY respectively. Thus, the important difference between the Wolfe and the Tabar classification concerns Tabar’s pattern 1, which is described in detail below.

Pattern 1 describes the three main characteristics of normal fibroglandular tissue: (1) evenly scattered 1–2 mm nodular densities, corresponding to normal terminal ductal lobular units; (2) Cooper’s ligament and concave parenchymal contour; and (3) oval-shaped/circular lucent areas, corresponding to fatty replacement, this resulting in a harmonious structure. Pattern 1 may evolve to pattern 2 following fatty replacement, or pattern 3, i.e. a retroareolar linear pattern, as a result of periductal elastosis or fatty involution. Wolfe completed his patterns description with a fifth pattern, QDY, which may be compared to Tabar pattern 1 (Wolfe, 1976). Wolfe states that the QDY pattern should be used for women below age 45 whose degree of dysplasia is not severe and that these patterns often regress with age to less dense patterns, Wolfe’s P2 or P1 (Wolfe, 1976). We combined patterns 1–3 into a low-risk group and patterns 4 and 5 into a high-risk group for analysis (Tabar and Dean, 1982; Bergkvist et al., 1987).

Prevalence odds ratios (ORs) were used to express the degree of association between mammographic patterns and
breast cancer risk factors. Each of the following factors was evaluated as a potential confounder of the risk factor/high-risk pattern relation: age, weight, and height. The odds ratios for each of these factors were estimated in both univariate and multivariate analyses for all women and also subdivided by menopausal status. A logistic regression model was used to allow for the effects of several potential confounders.

Statistical trend tests were obtained by creating an ordinal exposure variable with equally spaced scores and including it in the logistic regression model (Hosmer and Lemeshow, 1989).

Results

Table I displays selected attributes of the women at the time of the screening according to menopausal status. Premenopausal women were on average younger and were slightly younger at menarche and at first birth than post-menopausal women. More premenopausal women were parous, but they had, on average, fewer children than did post-menopausal women (Table I).

Patterns were classified for 3640 women as follows: 1659 as pattern 1, 857 as pattern 2, 401 as pattern 3, 354 as pattern 4 and 369 as pattern 5. Thus, 20% (723) of the women were classified as having a high-risk pattern. Table II displays the prevalence and crude odds ratio estimates of high-risk patterns by age and menopausal status. Premenopausal women were more likely than post-menopausal women to have a high-risk pattern (OR = 1.3, 95% CI 1.1–1.5). This association was present when stratified by age and was strongest in the youngest age group. Though younger women were more likely to have a high-risk pattern than older women, the association of age with pattern was weak or not present when stratified by menopausal status (Table II).

Weight was inversely and height positively associated with high-risk patterns and are together with age adjusted for in all analyses. A multivariate model that included terms for age, weight, height (all three continuous), menopausal status (premenopausal, post-menopausal), parity (0, 1–2, 3–4, 5 +) and age at first birth (<20, 20–24, 25–29, 30–34, 35 +) as independent variables and high-risk patterns as the dependent variable was fitted.

The odds ratio estimates of high-risk patterns according to reproductive and menstrual factors are shown in Tables III and IV respectively.

Table III shows that parous women were less likely to have high-risk patterns than nulliparous women (OR = 0.36, 95% CI 0.29–0.47) (Table III). Women having more than four children were 90% less likely to have a high-risk pattern than nulliparous women (OR = 0.09, 95% CI 0.04–0.16). Dose-response was evaluated among parous women. An ordinal trend test across the three levels of parity (1–2, 3–4, 5 +), displayed in Table III, yields a P-value of less than 0.001.

Table III shows that the ORs pertaining to age at first birth were highest among women who had their first child at an older age, controlling for parity. Nulliparous women were added as the last category in the same model, after age group 35 +. The results of this analysis showed that nulliparous women were more than twice as likely to have a high-risk pattern compared with women who had their first child in their teens (OR = 2.37, 95% CI 1.02–5.50). A statistical trend test for age at first birth (with five categories among parous women) adjusting for parity yielded a P-value less than 0.001. Adding the nulliparous women as the sixth category gave a similar result.

The trend with age at first birth was evident among both women with few (1 or 2) children (P = 0.0001) and women with many (3 +) children (P = 0.006). The trend with parity (three levels: 1–2, 3–4, 5 +) was also revealed among women with young (<24 years) age at first birth (P = 0.001) and among those with late (30 + years) age at first birth (P = 0.014). Table IV displays the relationship between age at menarche (four levels: <12, 12–13, 14–15, 16 +) and high-risk patterns stratified by menopausal status adjusted for age, height, weight and parity (Table IV). Among premenopausal women, those whose age at menarche was 16 + were more than twice as likely to have a high-risk pattern (OR = 2.4, 95% CI 1.3–4.5) than those whose age at menarche was less than 12 years. Among post-menopausal women, those whose age at menarche was 16 + were 80% less likely to have a high-risk pattern (OR = 0.2, 95% CI 0.1–0.6) than those with an early age at menarche. Dose-response was evaluated using the four levels of age at menarche displayed in Table IV. The trend between age at menarche and high-risk patterns was evident among both premenopausal (P < 0.001) and post-menopausal women (P = 0.015) (Table IV).

Table I  Selected attributes at screening by menopausal status given as mean (s.d.) and per cent, Tromsø, Norway

| Age (years) | Premenopausal n = 2903 | Post-menopausal n = 1337 |
|-------------|------------------------|---------------------------|
| 25–29       | 44.3 (3.6)             | 51.8 (4.2)                |
| Parous (%)  | 92.0                   | 87.1                      |
| No. of children | 2.4 (1.3)             | 2.6 (1.7)                |
| Age at first birth* (years) | 23.1 (4.2)           | 23.2 (3.9)                |
| Age at menarche (years) | 13.3 (1.4)          | 13.6 (1.4)                |
| Age at menopause* (years) | 46.5 (5.4)           |                          |

*Among parous women. 1Among post-menopausal women.

Table II  Prevalence (%) and crude odds ratio estimates of high-risk mammographic patterns* by age and menopausal status, Tromsø, Norway

| Age (years)   | Population | Premenopausal | Post-menopausal | Odds ratio† |
|---------------|------------|---------------|----------------|-------------|
| 40–45         | 1428 (20.3)| 1331 (21.0)   | 97 (11.3)      | 2.1 (1.1–4.4) |
| 46–50         | 1173 (20.1)| 824 (21.2)    | 349 (17.5)     | 1.3 (0.9–1.8) |
| 51–56         | 1039 (19.0)| 148 (25.0)    | 891 (18.0)     | 1.5 (1.0–2.3) |
| All           | 3640 (20.0)| 2303 (21.3)   | 1337 (17.4)    | 1.3 (1.1–1.5) |

*High risk = patterns 4 and 5. 1Post-menopausal women, reference category. 1Numbers in parentheses are 95% confidence interval.

Table III  Odds ratio estimates for high-risk mammographic patterns* according to reproductive factors surveyed at population screening, Tromsø, Norway

| Reproductive factors | High* risk | Low* risk | Odds ratio† | Trend test |
|----------------------|------------|-----------|-------------|------------|
| Parous               | No         | Yes       |             |            |
| No of children       |            |           |             |            |
| 0                    | 116        | 216       | 1.00        |            |
| 1–2                  | 322        | 1093      | 0.52 (0.40–0.68) | P < 0.001* |
| 3–4                  | 210        | 1160      | 0.29 (0.21–0.38) |            |
| 5+                   | 12         | 253       | 0.09 (0.04–0.16) |            |
| Age at first birth* (years) |            |           |             |            |
| <20                  | 60         | 475       | 1.00        | P = 0.001* |
| 20–24                | 293        | 1500      | 1.35 (0.98–1.84) |            |
| 25–29                | 171        | 558       | 1.81 (1.27–2.58) |            |
| 30–34                | 210        | 1200      | 2.51 (1.53–4.12) |            |
| 35+                  | 32         | 250       | 2.37 (1.23–4.56) |            |

*High risk, patterns 4 and 5. Low risk, patterns 1, 2 and 3 (reference category). 1Adjusted for age, menopausal status, weight and height. 1Numbers in parentheses represent 95% confidence interval. 1Trend test among parous women (three categories of parity). 1Also adjusted for number of children. 1Trend test among parous women (five categories of age at first parity).
Table IV Odds ratio estimates for high-risk mammographic patterns according to menstrual factors surveyed at population screening. Tromsø, Norway

| Menstrual factors | High risk | Low risk | Odds ratio | Trend test |
|-------------------|-----------|----------|------------|------------|
| Age at menarche<sup>1</sup> (years) | 29 | 155 | 1.00 | P = 0.001 |
| Age at menarche<sup>2</sup> (years) | 12–13 | 178 | 792 | 1.1 (0.7–1.7) |
| Age at menarche<sup>2</sup> (years) | 14–15 | 193 | 629 | 1.4 (0.9–2.1) |
| Age at menarche<sup>2</sup> (years) | 16+ | 38 | 67 | 2.4 (1.3–4.5) |

<sup>1</sup>High risk, patterns 4 and 5. <sup>2</sup>Low risk, patterns 1, 2 and 3 (reference category). <sup>3</sup>Adjusted for age, weight, height and number of children. <sup>4</sup>Among premenopausal women. Numbers in parentheses represent 95% confidence interval. <sup>5</sup>Among post-menopausal women.

To give more stable estimates of the association between age at menarche and high-risk patterns, age at menarche was divided in two categories: 13 years or less and more than 13 years. The directions of the associations were the same as indicated in Table IV. Among premenopausal women, those whose age at menarche was 13 years or less were 35% more likely to have a high-risk pattern (OR = 1.35, 95% CI 1.08–1.69), and among post-menopausal women those whose age at menarche was 13 years or less were 25% less likely to have a high-risk pattern (OR = 0.75, 95% CI 0.54–1.04) than those with a younger age at menarche.

Table IV shows that women with a later age at menopause were more likely to have high-risk patterns than those with an early menopause (Table IV). Stratified by age groups, women aged 45–52 years at menopause were 30% more likely (OR = 1.3, 95% CI 0.9–2.0) and those aged over 52 were 50% more likely (OR = 1.5, 95% CI 0.7–3.2) to have high-risk patterns than those having an early menopause (i.e. less than 45 years). A statistical trend test across the three levels described did not achieve statistical significance (P = 0.072).

Discussion

This study confirms that parity is inversely associated with high-risk mammographic patterns. In addition, an independent positive association of age at first birth and high-risk patterns is demonstrated. Age at menarche is positively associated with high-risk patterns among premenopausal women, whereas the inverse association is displayed among post-menopausal women. Furthermore, our results indicate an association between late age at menopause and high-risk patterns previously not shown. The study also suggests that menopausal status rather than age appears to be most closely related to mammographic patterns among perimenopausal women.

A limitation of our study is that the temporal relationship between the factors studied and the mammographic patterns is unknown. The use of recalled age at menarche, age at menopause and age at first birth may cause non-differential misclassification, and thereby attenuate the real association. We consider therefore our estimates to be conservative ones.

We attribute much of the consistency of the findings to the Tabar system in which one of the patterns previously classified as a high-risk is now classified as a low-risk pattern. The mammograms were classified by an experienced mammographer (LT) who had no knowledge of the risk factors surveyed, and we were also able to adjust for potential confounding variables. The study is population based, and the attenders did not differ from the non-attenders with respect to the risk factors studied (Gram and Slenker, 1992).

A causal interpretation of the association between reproductive factors and high-risk patterns is supported by the presence of a dose–response relation between the various levels of parity and age at first birth with high-risk patterns. These associations are present when stratified both by menopausal status and by each other. The effects are not confounded by weight or height as this has been adjusted for in the multivariate analyses.

Several studies have found an association with either parity or age at first birth and parenchymal patterns (Bergkvist et al., 1987; Saftlas and Szlko, 1987; Leinster et al., 1988; Brisson et al., 1989; De Stavola et al., 1990). However, only in the study by De Waard et al. (1984) is an independent effect of both aspects of reproductive life revealed, which remains after adjusting for Quetelet’s index.

Our study shows an association between age at menarche and high-risk patterns stratified by menopausal status adjusting simultaneously for parity, age, weight and height. One of the two studies listed in the review by Saftlas and Szlko (1987) also demonstrates a positive association between age at menarche and high-risk patterns. In a later analyses, expanded to include more than 5000 Guernsey women stratified by menopausal status, the positive association between age at menarche and high-risk patterns among premenopausal women was totally explained by adiposity. In post-menopausal women, the positive association remained statistically significant after adjusting for age, parity and Quetelet’s index (De Stavola et al., 1990). In another study of 5319 screeneees, there was no correlation between high-risk patterns and age at menarche for either menopausal category when breast size, weight, late age at first pregnancy, prior biopsy and history of cyclical breast pain were included in the model (Leinster et al. 1990). The positive association between age at menarche and high-risk patterns found among premenopausal women in our study and among post-menopausal Guernsey women may be due to chance.

Our study shows an association between age at menarche and high-risk patterns stratified by menopausal status adjusting simultaneously for parity, age, weight and height. One of the two studies listed in the review by Saftlas and Szlko (1987) also demonstrates a positive association between age at menarche and high-risk patterns. In a later analysis, narrow limits. We find no overall effect of age on high-risk patterns. However, at a given age, premenopausal women are at greater risk of high-risk patterns than post-menopausal women of the same age. Two other studies reported similar results (Grove et al., 1985; Leinster et al., 1988). In the study from Guernsey, the proportion of high-risk patterns was found to peak around menopause (De Stavola et al., 1990). Among the studies that did not stratify by menopausal status, the Swedish investigators reported a peak of high-risk patterns in the age group 46–50 years, whereas the other researchers found decreasing proportions of high-risk patterns with increasing age (Bergkvist et al., 1987; Saftlas and Szlko, 1987; Brisson et al., 1989; Bartow et al., 1990; Ciatto and Zappa, 1993).

Twenty per cent of the mammograms in our study were classified as high-risk patterns, while the corresponding figure in most studies using Wolfe’s classification is between 30% and 70% (Saftlas and Szlko, 1987; Ciatto and Zappa, 1993; Holowaty et al., 1993). All our high-risk patterns would be classified as such in the Wolfe system. However, one of our low-risk patterns (pattern 1) would most likely be classified as a high-risk pattern, i.e. either a P2 or a DY depending on the woman’s age according to the Wolfe system (Wolfe, 1976). Thus, the low proportion of high-risk patterns in our study is due not to inter- and intra-observer variations, but to this difference in the classification system. This should be kept in mind when the results from our study are compared with those of others.

The relation between reproductive and, among post-meno-
pausal women, menstrual factors and high-risk patterns displayed in the present study compares with those found in most, but not all, studies on breast cancer risk (Kelsey et al., 1993; La Vecchia, 1994). Our results concerning factors associated with high-risk parenchymal patterns agree fairly well with a recent study of factors predicting cumulative incidence of breast cancer. All reproductive and menstrual factors other than age at menarche appeared to be influential, and also premenopausal women were at greater risk of contracting breast cancer than post-menopausal women of the same age (Rosner et al., 1994).

When all women are analysed together our data show no relationship between age at menarche and high-risk patterns. Thus, the positive association with age at menarche and high-risk patterns found among premenopausal women was obscured by the inverse association found among post-menopausal women. Three case–control studies showed a similar effect of age at menarche on breast cancer risk when the women were stratified by menopausal status (Byers et al., 1985; Hilsop et al., 1986; Rautalaihti et al., 1993).

The intriguing aetiology and possible prevention of breast cancer have been discussed extensively in recent studies (Spicer and Pike, 1992; Gammon and John, 1993; Henderson et al., 1993; Pinkerton, 1993; Kelsey et al., 1993; Pike et al., 1993; Rosner et al., 1994). An early age at menarche and a late age at menopause are associated with greater exposure to ‘oestrogen together with progesterone’, which is the prevailing hypothesis on breast cancer risk. As noted by Pike et al. (1993), breast cancer incidence is special as there is a distinct slowing of the rate of increase around age 50, i.e. around the average age at menopause. We suggest that the mechanisms related to age at menarche affecting mammographic parenchymal patterns operate differently among pre- and post-menopausal women.

There is currently some controversy on whether or not parenchymal patterns should influence screening strategies (Ciatto and Zappa, 1993; Halowaty et al., 1993). Our results support the notion that reproductive and menstrual factors are involved in determining the mammographic parenchymal pattern among premenopausal women. This should not affect screening strategies or the way radiologists interpret mammograms. We believe patterns to be most useful as a means of investigating the aetiology of breast cancer and for testing hypotheses about potential preventive strategies.

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