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BRIEF REPORT

Reproductive factors associated with mammographic density: a Korean co-twin control study

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Abstract To determine the mechanism by which menstrual and reproductive factors are associated with the risk of breast cancer, we examined the relationships between mammographic density and known menstrual and reproductive risk factors for breast cancer. A co-twin control study was conducted with 122 pairs of monozygotic Korean female twins selected from the Healthy Twin study. Mammographic density was measured from digital mammograms using a computer-assisted method. Information on selected menstrual and reproductive factors was collected through a self-administered questionnaire. Within-pair differences for each mammographic measure were regressed against within-pair differences for each menstrual and reproductive risk factor with an adjustment for body mass index and other menstrual and reproductive factors. The percent dense area was inversely associated with the age at the first full-term childbirth (FFTB) and the number of live births, although the associations were marginally significant with an adjustment for BMI and other reproductive factors. The non-dense area was positively associated with the age at the FFTB and the number of live births. The absolute dense area was positively associated with the duration of breast feeding. The age at menarche was not associated with any component of the mammographic measures. This finding suggests that mammographic density can mediate the protective effect of greater parity against breast cancer, at least in part while age at menarche, age at the FFTB, and breast feeding do not exert their effects through mammographic density.

Keywords Breast feeding · Breast neoplasms · Mammography · Menarche · Parity

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Introduction

Menstrual and reproductive factors are likely associated with the risk for breast cancer through an influence on proliferation and maturation of the breast parenchyma [1]. Mammographic density reflecting proliferation of the breast parenchyma [2], is also a strong risk factor for breast cancer, which is very consistently observed across various ethnic populations [3–7].

Given the relationships of breast cancer with menstrual and reproductive factors and mammographic density, we hypothesize that mammographic density has a direct association with menstrual and reproductive factors, reflecting the cumulative exposure to those factors that influence breast cancer development. If so, mammographic density can be used as a surrogate marker for the effect of menstrual and reproductive factors on a breast.

Studies have shown that mammographic density is consistently associated with parity in the same direction as the association between breast cancer and parity [8, 9]. However, the evidence regarding the relationship between mammographic density and the age at menarche, age at first full-term childbirth (FFTB), and duration of breast feeding is inconsistent. To clarify the biologic mechanism by which reproductive factors and mammographic density are associated with the risk for breast cancer, further evaluation on the relationship between mammographic measures and reproductive factors is needed.

Very high levels of heritability are commonly reported for mammographic measures [10–12] suggesting that a genetic effect is the most influential factor for mammographic density. With increasing age, non-dense area increases, while the absolute dense area and percent dense area decrease [10]. Menstrual and reproductive factors may differ materially by generation. Women born later tend to experience menarche at a younger age, marry at an older age, have their FFTB at an older age, lactate less, and have a lower number of children [13, 14]. Therefore, in order to evaluate the association between mammographic measures and menstrual and reproductive factors more clearly, age and genetic factors should be taken into consideration, especially in a study with a cross-sectional design.

In this study we evaluated the relationship between mammographic density and menstrual and reproductive factors in Korean monozygotic (MZ) twin pairs in a co-twin control design. Through this co-twin control study, we completely excluded the effect of age and genetic factors.

Materials and methods

Subjects and study design

Study participants were 122 pairs of female MZ twins from the Healthy Twin study who had a mammogram during the first-wave survey between April 2005 and November 2007. The Healthy Twin study has been conducted as a part of the Korean Genome Epidemiology Study. Korean adult twins and their first-degree adult family members have voluntarily participated in the Healthy Twin study without ascertaining their health status. Details about study designs and protocols of this multicenter study have been previously published [15]. All of the procedures of the Healthy Twin Study have been standardized through the development of a standard protocol and training of research coordinators and research assistants.

Mammograms were obtained using a full-field digital mammography system (Senographe 2000D/DMR/DS, General Electric Medical System, Milwaukee, WI, USA). A single observer who was blinded to all identifying information measured the total area of the breast and the area of dense tissue using a computer-assisted thresholding technique (Cumulus) [16] in one cranio-caudal view of the right breast. Then, the non-dense area and percent dense area (PDA) were derived. The reliability of repeated measurements of mammographic density was assessed in a 10% random sample of repeats within reading sets and the estimated intra-class correlation coefficients for the total area, dense area, non-dense area, and PDA were 0.99, 0.98, 0.97, and 0.98, respectively.

Weight (kg) and height (cm) were measured in light clothing using a standardized scale and a stadiometer. Body mass index (BMI) was calculated as the weight divided by the height squared (kg/m^2). Information about menstrual and reproductive factors was obtained by self-administered questionnaire with additional face-to-face interviews in cases of incomplete or ambiguous responses.

The zygosity of twin pairs was identified by 16 short tandem repeat (STR) markers that include 15 autosomal STR markers and one sex-determining marker (Perkin Elmer, Waltham, MA, USA) in 67% of the twin pairs. For the remaining 33% of the twin pairs, zygosity was determined based on a self-administered zygosity questionnaire which was validated to be 94.3% accurate through a STR marker study [17].

All of the participants provided written informed consent. The study protocol was approved by the Korea Center for Disease Control and the Institutional Review board of the three participating centers (Samsung Medical Center, Pusan Paik Hospital, and Dankook University Hospital).

Statistical analyses

This study was conducted in a co-twin control study design. The within-pair differences in variables were calculated. To evaluate the association between mammographic measures and reproductive and menstrual factors, regression coefficients of within-pair differences in each mammographic measure against within-pair differences in age at menarche, the age at FFTB, number of live births, and total duration of breast feeding were estimated. At first, unadjusted coefficients were estimated, then the analysis was repeated with additional adjustment for BMI, or for other menstrual and reproductive factors. The final full model included an adjustment for BMI and other menstrual and reproductive factors. For some cases in which information on menstrual and reproductive factors was missing and differences in those variables could not be calculated, data imputation was performed with an average value of within-pair differences in the variable to prevent loss of power for regression analysis with adjustment for these variables. All of the analyses were performed using the SAS statistical package (SAS Institute, Cary, NC, USA).

Results

Table 1 shows the distribution of age, mammographic measures, BMI, menstrual factors, and reproductive factors. The mean age of twins was 39.6 years (SD, 7.4) and the age ranged between 29 and 73 years. Those twins with a higher PDA had a smaller total and non-dense mammographic area and a larger absolute dense mammographic area compared with their co-twins. There was no significant difference in BMI, menstrual factors, and reproductive factors between twins with a higher PDA and their co-twins with a lower PDA.

Table 2 shows the regression coefficients for the within-pair differences in mammographic measures against the within-pair differences for selected menstrual and reproductive factors. The difference in age at menarche had an inverse relationship with the difference in non-dense area when covariates were unadjusted. However, when the BMI and reproductive factors were adjusted, the relationship was no longer present. The difference in age at FFTB was positively associated with the difference in the non-dense area regardless of the adjustment for BMI or other factors. There was no association between the difference in the age at the FFTB and the difference in PDA, but a significant inverse association was observed when other menstrual and reproductive factors were additionally adjusted. There was a consistent positive association between the difference in the duration of breast feeding and the difference in the absolute dense area regardless of adjustment for BMI or other factors. The difference in the number of live births was positively associated with the difference in non-dense areas in an un-adjusted model, BMI-adjusted model, and menstrual and reproductive factor-adjusted model. However, the association was reduced to borderline significance in a fully adjusted model.

Discussion

In the present co-twin control study, we showed that reproductive factors are associated with mammographic measures. However, the associations were not in the same direction as those between breast cancer and reproductive factors. This study had strength in that the associations between mammographic measures and reproductive factors were evaluated with full consideration of age and genetic effects.

Although mammographic density has been most typically represented by the PDA, evaluation of factors associated with absolute dense and non-dense areas are also considered to be important for a better understanding of the etiology and potential pathways of breast cancer [18]. Many studies have reported that the absolute dense area is associated with breast cancer risk to a similar magnitude as the PDA [5, 19, 20], yet it is still unclear which component of the mammographic density measure best predicts the risk of breast cancer. In this study, we found that the reproductive factors (duration of breast feeding) associated with absolute dense area differed from those associated with PDA (the age at the FFTB and number of live births). The non-dense area and PDA were associated with the same reproductive factors, such as the age at the FFTB and the number of live births, but in an opposite direction. These findings suggest that each reproductive factor may

Table 1 Within-pair comparisons of selected factors in 122 pairs of twins by the level of the percent dense area of the mammographic measures

Variables	N	Percent dense area			P value*
		Overall (N = 244)	Higher (N = 122)	Lower (N = 122)	
Age at mammogram, mean (SD), years	244	39.6 (7.4)	39.6 (7.4)	39.6 (7.4)	1.00
Mammographic measures					
Total area, mean (SD), cm^2	244	97.8 (35.7)	94.7 (34.5)	101.0 (36.7)	0.17
Absolute dense area, mean (SD), cm^2	244	42.2 (21.6)	46.1 (22.6)	38.3 (19.8)	<0.01
Non-dense area, mean (SD), cm^2	244	55.6 (32.4)	48.6 (29.3)	62.7 (34.0)	<0.01
Percent dense area, mean (SD), %	244	45.3 (19.6)	50.5 (19.8)	40.0 (18.0)	<0.01
Body mass index, mean (SD), kg/m^2	244	22.7 (2.9)	22.5 (2.9)	22.9 (2.9)	0.25
Age at menarche, mean (SD), years	238	13.9 (1.5)	14.1 (1.5)	13.9 (1.5)	0.34
Age at first full-term childbirth, mean (SD), years	213	27.1 (3.2)	27.3 (3.1)	26.9 (3.3)	0.35
No. of live births, mean (SD), persons	244	1.65 (0.90)	1.63 (0.87)	1.67 (0.92)	0.72
Duration of breast feeding, mean (SD), months	207	12.0 (12.7)	10.3 (10.3)	13.6 (14.5)	0.06
Ever-use of oral contraceptives, N (%)	243	33 (14.0)	18 (14.9)	15 (12.3)	0.85
Ever-use of estrogen replacement, N (%)	243	7 (2.9)	4 (3.3)	3 (2.5)	0.71
Postmenopausal status, N (%)	244	27 (11.1)	14 (11.5)	13 (10.7)	0.84

* Obtained by paired t test

Table 2 Regression coefficients (95% CI)[a] of within-pair differences in mammographic measures against within-pair differences in selected risk factors

Selected factors	Absolute dense area	Non-dense area	Percent dense area
Unadjusted coefficients			
Age at menarche (years)	−1.26 (−3.04, 0.53)	−2.19 (−4.28, −0.10)§	0.06 (−1.21, 1.33)
Age at first full-term childbirth (years)	0.32 (−0.38, 1.02)	1.14 (0.25, 2.04)§	−0.47 (−1.04, 0.10)
Duration of breast feeding (months)	0.38 (0.19, 0.57)¶	0.21 (−0.03, 0.44)‖	−0.01 (−0.14, 0.13)
Number of live births (persons)	1.41 (−0.94, 3.76)	3.22 (0.51, 5.93)§	−1.24 (−2.87, 0.39)
Body mass index adjusted coefficients			
Age at menarche (years)	−0.89 (−2.65, 0.86)	−1.27 (−3.03, 0.50)	−0.18 (−1.43, 1.07)
Age at first full-term childbirth (years)	0.25 (−0.45, 0.94)	0.86 (0.12, 1.59)§	−0.40 (−0.96, 0.16)
Duration of breast feeding (months)	0.36 (0.17, 0.54)¶	0.14 (−0.06, 0.34)	0.01 (−0.12, 0.14)
Number of live births (persons)	1.08 (−1.21, 3.37)	2.48 (0.15, 4.81)§	−1.07 (−2.67, 0.54)
Other menstrual factors[b] adjusted coefficients			
Age at menarche (years)	−0.65 (−2.41, 1.11)	−1.22 (−3.30, 0.86)	−0.32 (−1.60, 0.97)
Age at first full-term childbirth (years)	0.21 (−0.55, 0.96)	1.16 (0.27, 2.05)§	−0.55 (−1.10, −0.002)§
Duration of breast feeding (months)	0.37 (0.18, 0.56)¶	0.12 (−0.10, 0.34)	0.04 (−0.10, 0.17)
Number of live births (persons)	0.08 (−2.31, 2.46)	2.84 (0.03, 5.65)§	−1.64 (−3.38, 0.10)‖
Fully[c] adjusted coefficients (95% confidence intervals)			
Age at menarche (years)	−0.39 (−2.12, 1.33)	−0.60 (−2.42, 1.21)	−0.47 (−1.74, 0.80)
Age at first full-term childbirth (years)	0.11 (−0.62, 0.85)	0.94 (0.16, 1.71)§	−0.50 (−1.04, 0.05)‖
Duration of breast feeding (months)	0.35 (0.17, 0.54)¶	0.08 (−0.11, 0.28)	0.05 (−0.09, 0.18)
Number of live births (persons)	−0.11 (−2.44, 2.21)	2.38 (−0.07, 4.82)‖	−1.52 (−3.24, 0.19)‖

‖ $P < 0.1$, § $P < 0.05$, ¶ $P < 0.01$

[a] Assessed by multiple linear regression analysis

[b] Age at menarche, age at first full-term childbirth, duration of breast feeding, and number of live births were adjusted

[c] Body mass index, age at menarche, age at first full-term delivery, duration of breast feeding, and number of live births were adjusted

act differently on breast parenchyma and are associated with breast cancer risk through different pathways.

The number of live births or parity has been shown to be inversely associated with mammographic density in previous studies that measured density either qualitatively [8, 21] or quantitatively [22, 23], with a rare exception [24]. In this study, the within-pair difference in the number of live births was positively associated with the within-pair difference in the non-dense mammographic area and inversely associated with the within-pair difference in the PDA with marginal significance when BMI, other selected reproductive factors, and age at menarche were considered. This finding is compatible with other studies which suggest that breast tissue aging slows down with successive pregnancies [25] and mammographic density can mediate the protective effect of greater parity against breast cancer, at least in part.

According to the Pike model of breast tissue aging, the FFTB slows down the rate of breast aging and an earlier age at the FFTB decreases the cumulative exposure to mammographically dense tissue [25]. Although exceptions exist [18, 22], the age at the FFTB has been positively associated with mammographic density in many studies [8, 9, 23, 26, 27]. In this study, the within-pair difference in the age at the FFTB was associated with the within-pair difference in the PDA inversely and with the difference in the non-dense area positively, which is in contrast to the finding from previous studies. We have reasoned that this discrepancy between studies may be related to study design. This co-twin control study completely eliminates the confounding by age and related birth cohort effects, which other study designs have not achieved.

Breast feeding is thought to be a protective factor against breast cancer in many epidemiologic studies through differentiation of breast tissue and reduction of the lifetime number of ovulatory cycles [28, 29]. During lactation, the increased level of prolactin stimulated by suckling [30] promotes cell proliferation in the breast [31]. However, it is less clear whether or not breast feeding is associated with mammographic density that reflects epithelial and stromal proliferation of a breast [22, 23, 27, 32]. Furthermore, studies investigating the relationship between the prolactin level and PDA have shown inconsistent results. A study reported a positive association between the prolactin level and the percent mammographic density in postmenopausal women [33], whereas another study reported an inverse association confined to premenopausal women [32]. In this study, the within-pair difference in the duration of breast feeding was positively associated with the within-pair difference in the absolute dense mammographic area alone, which does not support mammographic density mediating the association between breast feeding and breast cancer.

Even though earlier age at menarche is thought to increase the risk of breast cancer by increasing the lifetime exposure to estrogen [1], it is uncertain if age at menarche is associated with mammographic density based on the conflicting results of previous studies [18, 22, 23]. Most studies have not found an association between age at menarche and mammographic density [18, 23, 27, 32] and few studies have reported a positive association [22, 34]. In our study, the within-pair difference in age at menarche was not associated with the within-pair difference for any of the mammographic measures. It seems less likely that mammographic density mediates the inverse association between age at menarche and the risk for breast cancer.

Some limitations in this study should be considered. We measured mammographic density using digital mammography instead of film-screen mammograms that has been used in most of the studies evaluating the association between breast cancer risk and mammographic density. However, it is unlikely that our findings were affected by using digital mammography because digital mammography has been shown to be similar to or more sensitive than film-screen mammography in overall diagnostic value and in detecting breast cancer [35, 36]. Furthermore, all of the mammograms performed in this study were obtained using the same type of digital mammography equipment to eliminate any potential bias due to image processing. The information on menstrual and reproductive history was self-reported, which could have incurred bias to the study findings. However, information bias is unlikely because the information was collected before the study participants or research assistant were aware of the mammography data and there was no breast cancer case among participants.

In the present co-twin control study, the PDA was inversely associated with the age at FFTB and the number of live births, although the associations were marginally significant with an adjustment for BMI and other reproductive factors. The non-dense area was positively associated with the age at the FFTB and the number of live births. The absolute dense area was positively associated with the duration of breast feeding. With the exception of the number of live births, these associations were not in the same direction as the association between breast cancer and reproductive factors, which suggest that the age at the FFTB and breast feeding do not exert their effect through mammographic density.

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