Short Communication

Is There Overlap Between the Genetic Determinants of Mammographic Density and Bone Mineral Density?

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Abstract

Mammographic density and bone mineral density, risk factors for breast cancer and osteoporotic fractures, respectively, are both thought to reflect cumulative exposure to estrogen and are highly heritable. We asked if there was overlap between the genes that explain their variances. We studied 63 monozygous and 71 dizygous female twin pairs ages 38 to 71 years (mean, 50 years). Absolute and percent mammographic densities were measured by a computer-assisted method, and bone mineral density was measured at the lumbar spine, femoral neck, and forearm by dual energy X-ray absorptiometry. After adjusting for age, height, and weight, the within-person and cross-trait cross-twin correlations between the mammographic density and bone mineral density measures were between −0.09 and 0.16 (SEs, 0.07-0.09) and independent of zygosity (all P > 0.05). We conclude that there is little, if any, overlap between the genetic or environmental determinants of disease risk associated with these traits. (Cancer Epidemiol Biomarkers Prev 2005;14(9):2266–8)

Introduction

Mammographic density is the area of the two-dimensional representation of the breast on a mammogram that is radiographically dense and is presumed to represent connective and epithelial breast tissue. It is a well-established and strong risk factor for breast cancer, independent of age and other risk factors measured by questionnaires (1). Mammographic density itself can be changed by interventions involving hormones (2-4) and tamoxifen (5) and reproductive factors which affect exposure to endogenous estrogen and progesterone are associated with age-adjusted mammographic density (1). In premenopausal women, the proliferation of mammographic density is stimulated by estrogen and progesterone and is highest during the luteal phase of the menstrual cycle (6, 7). Therefore, it is possible that mammographic density is influenced by hormone-related risk factors for breast cancer. Furthermore, these factors are as yet unknown and may not be captured by questionnaire items that are presumed to be surrogates for exposure to hormones.

Bone mineral density is a two-dimensional measure of the attenuation of a weak X-ray beam through the body, is correlated with the amount of calcium in the bones, and is a risk factor for osteoporotic fractures (8). Estrogen plays an important part in the regulation of bone turnover, determination of peak bone mineral density, and age-related loss of bone mineral density (9). Bone mineral density has also been associated with reproductive factors that influence levels of endogenous estrogen, and decreases after menopause (9).

Both traits are highly heritable. Studies of twin pairs under the assumptions of the classic twin model suggest, and are supported by those of other close relatives, that genetic factors explain about 60% of the age-adjusted variance in mammographic density (10-14) and, depending on site, 50% to 80% of the age-adjusted variance in bone mineral density (15-19). Measurement error explains about 10% of mammographic density variance and <5% of bone mineral density variance, and the remainder is considered to be due to individual-specific environmental effects. We therefore asked if there was overlap in the genes that explain variation in these two traits.

Materials and Methods

We identified 63 monozygous and 71 dizygous female twin pairs who had participated in both a cross-sectional study of mammographic density conducted between 1995 and 1999 and a longitudinal study of bone mineral density conducted since 1990, recruited through the Australian Twin Registry and described in detail by Boyd et al. (13) for the mammographic density study and in Macninis et al. (20) and Flicker et al. (21) for the bone mineral density study. Mammographic density was measured by a computer-assisted method (22) and bone mineral density by dual energy X-ray absorptiometry (8). The study protocols were approved by the Human Research Ethics Committees at The University of Melbourne (mammographic density study) and the Clinical Research and Ethics Committee at the Royal Melbourne Hospital (bone mineral density study). All twins provided written informed consent for participation in each study.

Data from the mammographic density study (age at mammogram, percent mammographic density, mammographic density area, and self-reported height and weight) were merged with those from the bone mineral density study for the date closest to the date of mammography (age at bone scan, bone mineral density at the lumbar spine, femoral neck, and forearm,

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and measured height and weight). Twins were of ages 38 to 71 years (mean, 50; SD, 8). The mean absolute difference in age at measurement between the studies was 1.5 years (SD, 1.4).

The classic twin model decomposes the variance of a trait by considering the difference between, and relative magnitudes of, the trait correlations in monozygous and dizygous pairs. Under the assumption that the nongenetic determinants of the trait are shared within monozygous pairs to the same extent as they are shared within dizygous pairs, a greater correlation in monozygous pairs than in dizygous pairs is consistent with genetic factors explaining at least part of the trait variation (23).

The model can be extended to assess whether the genetic determinants of one trait overlap with the genetic determinants of another trait. To do this, one tests whether the correlation between one trait in one twin and the other trait in the other twin (the cross-trait cross-twin correlation) is greater for monozygous pairs than for dizygous pairs (24).

Models were fitted according to maximum likelihood theory under a multivariate normal model using the software FISHER (25). We log transformed mammographic dense area. The trait means were modeled as functions of the relevant measures of age, height, and weight. In previous analyses, we fitted models for mammographic density and bone mineral density measures and found evidence for a genetic component and an individual specific environmental component for each trait (e.g., refs. 13, 19, 21). All statistical tests were two sided.

### Table 1. Adjusted estimates, SEs, and P values of the within-twin cross-trait correlations between mammographic density and bone mineral density for all pairs, and, the cross-twin cross-trait correlations for monozygous and dizygous pairs

<table>
<thead>
<tr>
<th>Cross-trait correlations</th>
<th>Forearm bone mineral density</th>
<th>Femoral neck bone mineral density</th>
<th>Lumbar spine bone mineral density</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est.</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>Percent mammographic density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All within-twin</td>
<td>0.070</td>
<td>0.087</td>
<td>0.3</td>
</tr>
<tr>
<td>Monozygous cross-twin</td>
<td>0.033</td>
<td>0.091</td>
<td>0.2</td>
</tr>
<tr>
<td>Dizygous cross-twin</td>
<td>0.057</td>
<td>0.073</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Log dense area of mammogram

| All within-twin          | -0.099 | 0.087 | 0.1 | 0.046 | 0.087 | 0.5 | 0.048 | 0.087 | 0.4 |
| Monozygous cross-twin    | 0.022 | 0.079 | 0.8 | -0.085 | 0.074 | 0.3 | 0.004 | 0.075 | 0.9 |
| Dizygous cross-twin      | 0.031 | 0.077 | 0.7 | 0.003 | 0.081 | 0.9 | 0.029 | 0.080 | 0.7 |

**NOTE:** Adjusted for age at mammogram, age at bone scan, height, and weight. Est., estimates.

Figure 1. Cross-twin cross-trait scatterplots (A) and within-pair difference scatterplots (B) for the standardized residuals of age-, height-, and weight-adjusted percent mammographic density (PMD) versus lumbar spine bone mineral density (BMD) for monozygous and dizygous pairs.
Results

Table 1 shows that neither percent mammographic density nor log mammographic dense area was correlated with any of the bone mineral density measures, within pairs or across pairs, or in either zygosity group. Stratification by menopausal status gave similar results for the 57 pairs both premenopausal and the 58 pairs both postmenopausal (data not shown). As an illustration, Fig. 1 shows the lack of association between the age-, height- and weight-adjusted standardized residuals for percent mammographic density and lumbar spine bone mineral density for both monozygous and dizygous pairs using cross-twin cross-trait scatterplots and scatterplots of the within-pair differences in the two traits which account fully for age and in part for other potential confounding factors.

Discussion

Recently, Kerlikowske et al. (26) reported on a cross-sectional study which also found no correlation within an individual between percent mammographic density and bone mineral density at the hip or spine, overall and within subgroups. Our twin study has supported their null finding within twins and also found no correlation across twins. We had 80% power to detect at 0.05 (two-tailed) a true correlation of more than 0.2 or less than 0.2. There are both genetic and environmental determinants of variation in these two traits. Kerlikowske et al. (26) and our result of a null correlation between these two traits within an individual would not necessarily imply that there was no overlap of genetic factors; however, for that to be true, any association would have to be counteracted by individual-specific environmental factors (independent of zygosity) that act in the opposite direction in both traits so as to cause a negative (or positive) correlation between the two traits. However, because we observed no significant monozygous cross-trait cross-twin correlations, and no significant difference between monozygous and dizygous cross-trait cross-pair correlations, we conclude there is little, if any, overlap of genetic, or environmental, determinants of disease risk associated with these traits. The absence of any correlation between these two traits may be due to the manner in which they are affected by estrogen exposure. Bone mineral density is related to cumulative estrogen exposure whereas increases in mammographic density occur during the luteal phase of the menstrual cycle.

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References

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