Physical Activity and Mammographic Breast Density in the EPIC-Norfolk Cohort Study

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Physical inactivity and high mammographic breast density have both been associated with increased breast cancer risk. However, the association between physical activity and mammographic breast density remains inconsistent. In the European Prospective Investigation of Cancer (EPIC)-Norfolk population-based cohort study (United Kingdom), the authors investigated the cross-sectional association between physical activity level at baseline during 1993–1997 and breast density among 1,394 postmenopausal, cancer-free women. Usual physical activity was assessed by a brief, validated questionnaire. Percentage breast density was determined visually from mammograms by three trained radiologists using the Boyd six-category scale. The association between physical activity level and breast density risk category was examined. No statistically significant association between physical activity and percentage breast density was observed in the unadjusted or adjusted regression models. A suggested increase in breast density for the most active women in the unadjusted regression analysis (odds ratio = 1.13, 95% confidence interval: 0.71, 1.80) was reversed after inclusion of body mass index and reproductive and lifestyle variables (odds ratio = 0.78, 95% confidence interval: 0.45, 1.34). The lack of an association between physical activity and percentage breast density suggests that an association between physical activity and breast cancer risk is unlikely to be mediated through an effect on mammographic breast density.

breast; breast neoplasms; exercise; mammography; motor activity

Abbreviations: BMI, body mass index; EPIC, European Prospective Investigation of Cancer.

A number of epidemiologic studies have shown that the magnitude of risk independently associated with high mammographic breast density exceeds that of all breast cancer risk factors other than germline mutations of BRCA1/2, with two- to sixfold risk increases detected across studies (1). Breast density varies both between and within an individual; approximately 60 percent of the interindividual variation is inherited (2), and density is also modified by a number of nongenetic factors. Since changes in breast density can be observed noninvasively and can occur in the same tissue...
MATERIALS AND METHODS

Participants in this study are part of the population-based European Prospective Investigation of Cancer (EPIC)-Norfolk cohort (15). The EPIC-Norfolk cohort comprises 30,445 residents of Norfolk, United Kingdom, aged 40–74 years, and is part of the larger 10-country EPIC-Europe study (16). All eligible individuals identified from participating general practitioner registers were recruited by postal invitation, and informed consent was obtained from all participants. Baseline examination from 1993 to 1997 consisted of a clinic visit for a health examination that included anthropometric measurements and blood sampling as well as completion of a detailed questionnaire to assess health and lifestyle factors. Ethical approval was received from the Norwich Local Research Ethics Committee.

Trained nurses examined all study participants at the clinic visit. Height, weight, waist circumference, and hip circumference were measured in centimeters. The ratio of waist circumference to hip circumference was determined, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

The health and lifestyle questionnaire assessed self-reported history of breast cancer, registered cancer status, and family history of total cancer and of breast cancer in parents and siblings. Smoking status was evaluated by yes/no responses to the following questions: Have you ever smoked as much as one cigarette a day for as long as a year? and Do you smoke cigarettes now? Occupation-based social class, educational level, and marital status were also assessed via questionnaire.

Alcohol intake and consumption of total fat, fruit, vegetables, fiber, and red meat were determined by a food frequency questionnaire and were quantified in grams per day. Total energy intake, also estimated by food frequency questionnaire, was quantified in kilocalories per day. Reproductive history included assessment of menopausal status, age at menopause, age at menarche, age at first livebirth, parity, oral contraceptive use, and hormone replacement therapy use.

Physical activity over the past year was assessed by a brief, validated questionnaire for both occupational (sedentary, standing, physical work, heavy manual work) and leisure-time (cycling, exercise) activities to compute an index of habitual activity (13). Frequency (hours per week) of leisure-time physical activity during both summer and winter was measured, and average daily physical activity was calculated as total hours per week of physical activity divided by 7. On the basis of this average activity score, individuals were assigned to one of four physical activity categories: inactive (sedentary job, no recreational activity); moderately inactive (sedentary job, <0.5 hours per day recreational activity or standing job, no recreational activity); moderately active (sedentary job, 0.5–1.0 hours per day recreational activity or standing job, <0.5 hours per day recreational activity or physical job, no recreational activity); and active (sedentary job, >1 hour per day recreational activity or standing job, >1 hour per day recreational activity or physical job with some recreational activity or heavy manual job).

Mammograms were obtained and mammographic breast density was analyzed, as previously reported (17). Percentage breast density is a measure of the relative proportion of dense fibroglandular and adipose tissues in the breast, determined by the radiographic contrast between dense tissue that appears light on the mammogram and the darker, radiolucent fat. Briefly, four mammograms for each participant (mediolateral oblique and cranio-caudal views) were examined by three experienced radiologists who determined one density value for each breast by using the Boyd six-category scale (18). This process resulted in three density values (one from each reader) for the left breast and three density values for the right breast. The average of these six density readings was used as a summary mammographic density value for each participant. Repeatability of the breast density estimates was assessed, and values of weighted kappa statistics varied between 0.52 and 0.68.

In the present analysis, we included women who were postmenopausal and did not report diagnosed cancer (other than nonmelanoma skin cancer) at baseline. Of the 1,881 women who met these inclusion criteria, physical activity data and mammograms were available for 1,427. Of these 1,427 eligible women, 33 were excluded because of menopausal status (<2 years postmenopausal), leaving 1,394 women for analysis. A total of 1,292 women for whom data were available on all potentially confounding variables were included in the final model.

Logistic and multiple logistic regression analyses examined the association between physical activity level and risk category of percentage breast density. The reference category for all regression models was the “inactive” group, corresponding to the lowest level of physical activity. Low-risk breast density was determined as a percentage breast density less than 50 percent, and women with a percentage from which breast cancers arise, breast density may serve as a surrogate marker for breast cancer risk (3). Higher levels of physical activity are associated with a significantly lower incidence of breast cancer (4), and each additional hour of recreational activity per week is reported to reduce breast cancer risk by 6 percent (5). This association is more consistent among postmenopausal women and is independent of differences in body mass (5).

Evidence of an association between physical activity and mammographic breast density is inconsistent and limited to date. To our knowledge, only seven studies have investigated this relation; two reported borderline significance for lower breast density with physical activity (6, 7), four reported no association between breast density and overall physical activity (8–11), and one found that high levels of physical activity were significantly associated with lower breast density in a subgroup of obese, postmenopausal women (12). The observed heterogeneity of results from previous studies may be explained by differences in both the characteristics of the populations assessed and the methods used for measuring physical activity and breast density.

We evaluated the association between physical activity and percentage breast density in a large, population-based cohort by using a validated, predictive physical activity index (13, 14) and a semiquantitative assessment of percentage breast density from mammography.
breast density greater than or equal to 50 percent were classified as high risk (19). Potential correlates and confounders of the physical activity—mammographic density association were examined by analysis of variance, and collinearity among covariates was assessed by likelihood ratio models. The multivariate-adjusted model included the following covariates: BMI, age at mammogram, parity, energy intake, alcohol intake (continuous); hormone replacement therapy (current, former, never user); educational level (0 = less than compulsory O-level education up to age 16 years or no qualifications; 1 = compulsory O-level education up to age 16 years or equivalent; 2 = optional A-level education up to age 18 years or equivalent; 3 = degree or equivalent); smoking status (current, former, never smoker); and age at first birth (nulliparous; age 16–19, 20–24, 25–29, 30–34, ≥35 years). Effect modification by age at mammogram, BMI, parity, hormone replacement therapy use, and educational level was examined by likelihood ratio models.

Hypothesis tests were conducted at the 0.05 significance level, and all p values reported in this paper are two-sided. All analyses were performed with the statistical software package Stata (Stata Statistical Software, release 9.1; Stata Corporation, College Station, Texas).

RESULTS

Participants were an average age of 61.8 years at the baseline assessment and 63.5 years at time of mammogram (table 1). The majority did not have a family history of breast cancer, and the prevalence of current cigarette smoking was low (<8.0 percent). With respect to other breast cancer risk factors, most women were parous, with only 15.7 percent reporting nulliparity, and the majority experienced the first birth prior to age 30 years. The mean percentage breast density was 25.8 percent, and nearly 30 percent of the participants were classified in the lowest level of physical activity.

Older women and women with fewer children were less active than their counterparts (table 2). Active women were leaner and also reported higher energy intake than inactive participants (2,037 kcal compared with 1,873 kcal, p = 0.003). Concurrent with prior reports, older women and those who had higher body mass indices, were current users of hormone replacement therapy, gave birth to more children, or gave birth earlier in life had a lower percentage mammographic breast density (data not shown).

Percentage breast density varied slightly across levels of physical activity (table 2), although no overall association between physical activity level and mean unadjusted percentage breast density was detected (F = 1.02, p = 0.43). The majority of the population was classified as having low-risk percentage breast density, and the greatest proportion of dense breasts was evident among the most active women (table 3). Although the unadjusted regression model suggested an increased percentage breast density for the most active compared with inactive women, the association between physical activity level and risk category of percentage breast density was reversed and remained nonsignificant after adjustment for BMI and additional correlates and potential confounders (table 4). In the final model, physical activity explained less than 1 percent of breast density variance, with BMI accounting for the majority of the variance. Data were also analyzed by using 25 percent breast density as the cutoff to differentiate between high- and low-risk percentage breast density because of the relatively low mean percentage breast density (25.8 percent). However, the logistic regression analyses were insensitive to alterations in cutpoints; therefore, data are not shown.

DISCUSSION

This cross-sectional study did not detect an overall association between physical activity and percentage mammographic breast density in postmenopausal women. A suggested trend of increased breast density for the most active women in unadjusted analyses was reversed after adjustment for body mass and other covariates.

Our results are in agreement with four previous studies in which no overall association was observed between physical activity and breast density. Siozon et al. (10) reported that neither percentage mammographic breast density nor absolute mammographic density in 375 US-born women aged 35–64 years was significantly associated with recreational physical activity assessed by recall calendar. Similar to our results, this previous study (10) reported a trend between increasing hours of strenuous lifetime physical activity and higher percentage breast density among women older than 50 years of age after adjustment for several potential factors.
confounding factors. However, the association was attenuated and no longer statistically significant after further adjustment for BMI.

A study of 224 women with benign breast biopsies and 504 women recruited at routine mammogram to the Mammograms and Masses Study reported on the association between recreational physical activity and various measures of breast density (dense area, nondense area, total area, and percentage density) (11). In the total study population of 728 pre- and postmenopausal, breast-cancer-free women, a statistically significant decrease in both percentage breast density and absolute dense area with high physical activity was observed compared with the reference category and remained statistically significant after adjustment for BMI. However, compatible with our results, results from that study showed a statistically significant increase of 1.33 units in percentage density per additional metabolic-equivalent hour of “mild exercise” among the 504 volunteers recruited during routine mammogram screening. Moreover, this association remained evident following adjustment for BMI and other covariates.

In a recent study of 620 pre- and postmenopausal women aged 49–68 years in the Dutch EPIC cohort, no significant association was found for combined occupational/recreational physical activity and percentage or absolute mammographic breast density (8). Subgroup analysis revealed a lack of association among both pre- and postmenopausal women. This study (8) utilized the EPIC physical activity questionnaire used in the present study.

A sizable study of 1,900 women aged 40–93 years did not detect an association between usual physical activity determined by a single telephone interview question and percentage breast density among either pre- or postmenopausal women (9). However, the women included in this analysis were first-degree relatives of women diagnosed with breast cancer; therefore, the result may not apply to all women.

A study by Irwin et al. (12) reported a significant increase in percentage breast density with increased physical activity specific to lean, premenopausal women and also observed a contrasting significant decrease in both percentage breast density and absolute dense area with high physical activity for obese, postmenopausal women. This relation was present among individuals in the highest levels of sport and recreational physical activity compared with the reference category and remained statistically significant after adjustment for potential confounding factors. However, no significant overall association was detected between total physical activity or sport/recreational physical activity and either percentage breast density or absolute dense area, but the 474 study participants were breast cancer survivors, and the analysis examined physical activity and mammographic density 1 year prior to diagnosis. Therefore, this study sample differed from the general population.

In a further study of 439 breast cancer survivors, the dense breast area of active (≥11 metabolic-equivalent hours/week), obese (BMI ≥30 kg/m²) women was statistically significantly smaller than that observed in inactive, lean women (20). No corresponding association was observed for percentage breast density or for nonobese women. This study suggests that an association between physical activity and breast density may be subgroup specific, although no effect modification by BMI was detected in our study.

Gram et al. (6) found a borderline significant reduction in high-risk mammographic breast patterns assessed by the

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**TABLE 2. Characteristics of the study population by level of physical activity at baseline (n = 1,394 women), EPIC-Norfolk cohort, United Kingdom, 1993–1997**

<table>
<thead>
<tr>
<th>Physical activity quartile</th>
<th>Mean</th>
<th>SD*</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive (n = 417)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at mammogram (years)</td>
<td>64.0</td>
<td>4.5</td>
<td>63.4</td>
<td>4.6</td>
<td>63.1</td>
<td>4.5</td>
<td>62.9</td>
<td>4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol intake (units/day)</td>
<td>5.2</td>
<td>7.9</td>
<td>5.7</td>
<td>7.2</td>
<td>5.0</td>
<td>7.2</td>
<td>5.9</td>
<td>7.7</td>
<td>0.684</td>
</tr>
<tr>
<td>Energy intake (kcal/day)</td>
<td>1,872.6</td>
<td>521.1</td>
<td>1,897.1</td>
<td>507.7</td>
<td>1,897.3</td>
<td>526.9</td>
<td>2,037.2</td>
<td>581.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.9</td>
<td>4.4</td>
<td>26.2</td>
<td>4.0</td>
<td>25.8</td>
<td>3.7</td>
<td>25.7</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage breast density</td>
<td>24.7</td>
<td>21.9</td>
<td>26.5</td>
<td>22.4</td>
<td>24.9</td>
<td>21.6</td>
<td>27.9</td>
<td>22.7</td>
<td>0.431</td>
</tr>
<tr>
<td>Parity</td>
<td>1.95</td>
<td>1.39</td>
<td>2.01</td>
<td>1.26</td>
<td>2.12</td>
<td>1.19</td>
<td>2.16</td>
<td>1.18</td>
<td>0.028</td>
</tr>
</tbody>
</table>

*EPIC, European Prospective Investigation of Cancer; SD, standard deviation; HRT, hormone replacement therapy.
† Group-wise comparisons were performed by analysis of variance for continuous variables (age at mammogram, alcohol intake, energy intake, body mass index, parity) and by chi-squared tests for categorical variables (HRT, smoking status, educational level, social class).
‡ One unit of alcohol is equivalent to 8 g.
TABLE 3. Proportion (%) of the study population within risk categories of percentage mammographic breast density, by level of physical activity at baseline (n = 1,394 women), EPIC-Norfolk cohort, United Kingdom, 1993–1997

<table>
<thead>
<tr>
<th>Category (%) breast density</th>
<th>Physical activity level</th>
<th>Inactive</th>
<th>Moderately inactive</th>
<th>Moderately active</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (&lt;20)</td>
<td></td>
<td>53.7</td>
<td>49.1</td>
<td>51.5</td>
<td>51.8</td>
</tr>
<tr>
<td>Moderate risk (&gt;20–50)</td>
<td></td>
<td>31.2</td>
<td>34.8</td>
<td>33.0</td>
<td>31.4</td>
</tr>
<tr>
<td>High risk (&gt;50)</td>
<td></td>
<td>15.1</td>
<td>16.2</td>
<td>15.5</td>
<td>16.8</td>
</tr>
</tbody>
</table>

* EPIC, European Prospective Investigation of Cancer.

TABLE 4. Logistic regression of percentage breast density by level of physical activity at baseline (n = 1,394 women), EPIC-Norfolk cohort, United Kingdom, 1993–1997

<table>
<thead>
<tr>
<th>Physical activity level†</th>
<th>Odds ratio‡</th>
<th>95% confidence interval</th>
<th>p value for test of trend</th>
<th>Odds ratio§</th>
<th>95% confidence interval</th>
<th>p value for test of trend</th>
<th>Odds ratio¶</th>
<th>95% confidence interval</th>
<th>p value for test of trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Moderately inactive</td>
<td>1.08</td>
<td>0.76, 1.55</td>
<td>0.71, 1.80</td>
<td>1.03</td>
<td>0.902</td>
<td>0.825</td>
<td>0.70, 1.50</td>
<td>0.50, 1.39</td>
</tr>
<tr>
<td></td>
<td>Moderately active</td>
<td>1.03</td>
<td>0.68, 1.56</td>
<td>0.71, 1.80</td>
<td>0.914</td>
<td>0.58, 1.39</td>
<td>0.882</td>
<td>0.58, 1.39</td>
<td>0.50, 1.39</td>
</tr>
<tr>
<td></td>
<td>Active</td>
<td>1.13</td>
<td>0.71, 1.80</td>
<td>0.71, 1.80</td>
<td>0.825</td>
<td>0.50, 1.39</td>
<td>0.882</td>
<td>0.50, 1.39</td>
<td>0.50, 1.39</td>
</tr>
</tbody>
</table>

* EPIC, European Prospective Investigation of Cancer.
† Inactive was considered the reference category.
‡ Univariate model (n = 1,394).
§ Adjusted for body mass index (n = 1,331).
¶ Adjusted for age at mammogram, body mass index, parity, age at first birth, smoking status, hormone replacement therapy, educational level, total energy intake, and alcohol intake (n = 1,292).

While the mechanism by which physical activity may affect breast density remains unresolved, it is postulated that an effect on adiposity and/or sex hormones mediates changes in breast density. This hypothesis is biologically plausible, because a high level of exogenous or endogenous hormones is associated with increased risk of breast cancer (28, 29), and direct associations have been observed for both exogenous and endogenous steroid hormone levels and changes in breast density (30–33). Notably, hormone replacement therapy (particularly formulations of combined estrogen/progesterin) has been shown to increase breast density (30) and to delay involution, the age-related transition from dense to fatty breasts (31), whereas the selective design of the study limited our ability to discern temporality of an association. Only a randomized controlled trial of the effect of exercise on breast density would delineate the true nature of the association.

However, if a high dose of activity is required for an effect on breast density, the low prevalence of active women in our population (<14 percent) may have precluded observation of an effect. The most effective dose of physical activity for lower breast cancer risk has yet to be determined, and assessment of dose is limited by the lack of physical activity measures that comprehensively evaluate all parameters of activity (including intensity, frequency, duration, time of life, and domain). Although measurement error is a possibility in any self-reported data, the index of physical activity we used is reliable, valid (13), and predictive of all-cause mortality and incidence of cardiovascular disease in the EPIC-Norfolk cohort (14). This tool offers an advantage over many prior studies of the physical activity–percentage breast density association because only three studies used validated methods of physical activity measurement (6, 8, 12). Moreover, inclusion of occupational activity as well as recreational physical activity strengthens the current study.

We used percentage mammographic breast density as the outcome of this study. However, a number of studies have proposed that the total area of dense tissue (22–24) or the volume of densities (25) may provide a more accurate measure of breast cancer risk. Percentage breast density measures the amount of dense, epithelial and stromal tissue relative to lucent, fatty tissue and may therefore be affected by breast size. Yet, percentage density is highly correlated with other methods of mammographic density assessment and can be readily determined by trained radiologists with high repeatability and little need for extra equipment (26).

We used a visual scoring method and the Boyd classification (18) to yield a semicontinuous measure of percentage dense tissue. Although advanced techniques in digitized mammogram assessment may offer some benefit in reducing subjectivity (18), and computer-assisted techniques are currently considered the “gold standard,” qualitative assessment is more practical for application in clinical practice because it is more time efficient and cost-effective. Furthermore, breast density was scored by experienced, trained radiologists, and reliability among readers in the current study was acceptable. A recent study of the inter- and intraobserver variability of breast density scoring by visual assessment reported that subjective methods are reliable and feasible, particularly if observers are well trained (27).
estrogen receptor modulator tamoxifen has been observed to reduce breast density (32). Some studies have reported that endogenous estrone and estradiol are directly associated with mammographic density (33), although other studies, including one in the EPIC-Norfolk population, have failed to detect a significant association between endogenous sex hormones and percentage breast density (17, 34).

Moreover, moderate to vigorous physical activity is associated with lower levels of circulating sex hormones (35–37) as well as higher levels of sex hormone-binding globulin (38). However, among premenopausal women, the association is less consistent (39–41); in contrast to many previous observational studies that have detected inverse associations between high levels of activity and various sex hormones before menopause (4, 42), a recent randomized controlled study of 32 premenopausal women did not detect any change in 2-hydroxyestrone or 16α-hydroxyestrone after a 12-week physical activity intervention (43).

The concentration of circulating sex hormones may be indirectly affected by changes in adipose tissue consequent to high levels of physical activity (44). This possibility is particularly relevant for postmenopausal women, because estrogens are produced primarily by aromatization of androgens in adipose tissue following menopause (45, 46). In a recent study, McTiernan et al. (36) observed significantly lower estrone and estradiol levels in association with self-reported physical activity in postmenopausal women, and a subgroup of the most lean, active women exhibited the most pronounced decreases in estrone and estradiol. A recent exercise intervention among postmenopausal women consisting of 5 days per week of 45 minutes of moderate-vigorous–intensity exercise resulted in significantly decreased estrone, estradiol, and free estradiol after 3 months when these women were compared with controls (35). However, this effect was limited to those women who experienced a reduction in percentage of body fat and was not significant after 12 months of the intervention.

Interestingly, body weight and BMI are inversely associated with breast density because lean, active women display increased percentage density (47, 48). This observation highlights the influence of body composition as a negative confounder of the physical activity–breast density association.

A suggested positive association between physical activity and percentage breast density was explained by BMI in our study. Although no statistically significant association between physical activity and percentage breast density was observed, the most active women had a significantly reduced BMI (p < 0.001). Furthermore, a recent study of postmenopausal women in the EPIC-Norfolk population detected significant inverse associations between increasing activity level and circulating testosterone and estradiol and a significant positive association with sex hormone-binding globulin (38). Thus, it is apparent that the women in the current study achieved a level of physical activity sufficient to influence adiposity and sex hormone concentrations, without a corresponding effect on mammographic breast density. The lack of an overall association between physical activity and percentage breast density implies that physical activity influences breast cancer risk independently from mammographic breast density.

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Conflict of interest: none declared.

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