Published in final edited form as:
Med Sci Sports Exerc. 2013 August ; 45(8): 1515–1523. doi:10.1249/MSS.0b013e318289a7f8.

Adolescent and Young Adult Exposure to Physical Activity and Breast Density

Kelley Pettee Gabriel[1], **Catherine Klifa**[3], **Adriana Pérez**[2], **Andrea M. Kriska**[4], **Robin R. High**[5], **Linda Snetselaar**[6], and **Joanne F. Dorgan**[7]

[1]Division of Epidemiology, Human Genetics and Environmental Sciences, University of Texas Health Science Center in Houston, School of Public Health – Austin Regional Campus, Austin, TX

[2]Division of Biostatistics, University of Texas Health Science Center in Houston, School of Public Health – Austin Regional Campus, Austin, TX

[3]Dangeard Group, Mill Valley, CA

[4]Department of Epidemiology, University of Pittsburgh, Pittsburgh, PA

[5]Department of Biostatistics, University of Nebraska Medical Center, Omaha, NE

[6]Department of Epidemiology, University of Iowa, Iowa City, IA

[7]Fox Chase Cancer Center, Philadelphia, PA

Abstract

Purpose—To examine the role of early lifetime exposure to physical activity on magnetic resonance imaging (MRI) determined breast density measures.

Methods—Associations of adolescent [high school (ages 14–17 years) and early adulthood [post high school (ages 18–21 years) and past year] leisure-time physical activity, as well as a principal component score including all three estimates, were examined with percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) in a cross-sectional analysis of 182 healthy women, aged 25–29 years enrolled in the Dietary Intervention Study in Children Follow-up Study (DISC06). Generalized linear mixed (GLM) models were used to examine associations after adjustment for relevant covariates for the entire analytic sample. Analyses were repeated in nulliparous women and hormonal contraceptive non-users.

Results—Physical activity during high school and post high school were not statistically significantly related to %DBV or ADBV in multivariable models. Past year physical activity was positively related to %DBV in the unadjusted and partially adjusted models ($p<0.001$ and $p=0.01$, respectively) that did not adjust for body mass index (BMI). After additional adjustment for childhood and early adulthood BMI, this association became non-statistically significant. The relation between past year physical activity and ADBV was not statistically significant. These findings were similar in non-users of hormonal contraceptives. No statistically significant

---

Corresponding Author: Kelley Pettee Gabriel, Assistant Professor, University of Texas Health Science Center at Houston, School of Public Health - Austin Regional Campus, Division of Epidemiology, Human Genetics, and Environmental Sciences, 1616 Guadalupe Street, Suite 6.300, Austin, TX USA 78701, Office: 512-391-2525, Fax: 512-482-6185, Kelley.P.Gabriel@uth.tmc.edu.

Conflict of Interest/Financial Disclosure: None

No authors report any conflict of interest. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

relationships were found in nulliparous women or between the principal component score and %DBV or ADBV.

Conclusion—Results from this study are consistent with previous research suggesting that physical activity during adolescence and early adulthood is unrelated to breast density.

Keywords

motor activity; breast composition; young adult; childhood

Introduction

Adolescence represents an important time for breast development. During puberty, under the influence of estrogens and progesterone mammary ducts lengthen and branch and terminal duct lobular units form (32). Full differentiation of the mammary gland takes several years and will not take place unless pregnancy and lactation occur (37). Breast carcinogenesis primarily occurs in terminal duct lobular units and is characterized by a high proliferative rate (36). The number and proliferative state of epithelial cells enhances the probability of genetic damage and increased risk of breast cancer (26).

Physically active women have a 25–30% lower risk for breast cancer when compared to their sedentary counterparts (14). One proposed mechanism by which physical activity supports breast health is through the disruption of the hypothalamic-pituitary-ovarian (HPO) axis (15, 37). This disruption to the HPO axis causes a reduction in the cumulative exposure to endogenous sex hormones as a consequence of changes to menstrual patterns (14). It has been suggested that lower sex hormone levels associated with higher physical activity levels causes a decline in the proliferation of breast epithelial cells (13). Therefore, physical activity during adolescence and early adulthood, prior to the complete differentiation of the breast, could be particularly important for reducing risk of breast cancer across the lifespan.

The relative amount of dense breast tissue, which is composed of ductal epithelium and stroma (6) is a strong and independent risk factor for breast cancer (5, 7) and is also influenced by hormones and hormonal interventions (26). Therefore, the relation between physical activity and lifetime risk of breast cancer could be mediated through favorable changes to breast density. Several studies to date have examined the relationship between physical activity and breast density; with the majority reporting a statistically null association (39). However, three previous studies have shown a statistically significant inverse relationship between physical activity and breast density measured via mammography in postmenopausal women with (17, 18) and without a previous breast cancer diagnosis (25). In studies including a mixed population with regards to menopausal status, one study including pre- and post-menopausal women found a positive association between mild (i.e., light intensity) exercise and mammographic breast density; however, no statistically significant association was found with moderate or strenuous exercise (30). In a longitudinal analysis of the Study of Women Across the Nation (SWAN), a one unit increase total physical activity reduced the decline in percent mammographic density by 0.09% per year or 0.5% over six years (8). However, this was explained by a change in the non-dense breast area, or fat, and not the dense breast area.

Differences in results across studies could be explained by heterogeneity in methods related to the (a) selected study design, (b) targeted sample population, and (c) measurement of physical activity and breast density (31). It has been suggested that breast tissue composition, during early breast development, could be important for understanding later breast cancer risk. In previous studies, breast density was measured exclusively via mammography; therefore, study populations for these studies have primarily consisted of older women (aged ≥ 40 years). This is an important limitation for studies examining the role of early-life physical activity exposures on breast composition since participants are required to recall physical activity several decades in the past. The current study improves upon prior research by examining the role of leisure-time physical activity levels from adolescence to early adulthood on magnetic resonance imaging (MRI) determined percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) in a well-characterized sample of women aged 25–29 years. This is particularly important given that breast density was measured at a young age, which for most of the analytic sample was prior to terminal differentiation of the breast that occurs following pregnancy and lactation. Based on the proposed biological plausibility, it was hypothesized that adjusted for adiposity, early life exposure to physical activity will be inversely related to both %DBV and ADBV in younger women.

Methods

Study Design

The Dietary Intervention Study in Children (DISC), a multi-center randomized controlled trial sponsored by the National Heart, Lung, Blood Institute, was designed to test the safety and efficacy of a dietary intervention to reduce serum low-density lipoprotein cholesterol (LDL-C) levels in children with elevated LDL-C. The design and results of the DISC Study have previously been reported (9, 10). Briefly, between 1988 and 1990, 663 children (301 girls and 362 boys) aged 8–10 years with elevated LDL-C levels were recruited at one of six clinical centers and randomized to either a behavioral dietary intervention or usual care control group. Planned intervention continued until 1997 when the mean age of study participants was 16.7 years. In 2006–08, the DISC06 Follow-up Study (12) was conducted to evaluate the long term effects of the diet intervention on biomarkers associated with breast cancer risk in female participants. Assent was obtained from DISC participants and informed consent was obtained from their parents/guardians prior to randomization and informed consent was obtained from the participants prior to the DISC06 visit. The original and follow-up DISC protocols were approved by Institutional Review Boards at all participating clinical centers. Exempt status for this secondary data analysis was also obtained from the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects.

Study Participants

All 301 female participants randomized in DISC were invited to participate in the DISC06 Follow-up visit, of which 260 (86.4%) participated. The remaining 41 women could not be located or declined participation. When compared to those participating in the DISC06 Follow-up visit, those not attending this visit were slightly older at randomization (9.3 ± 0.6 versus 9.0 ± 0.6 years; $p = 0.005$); however, BMI was not statistically significantly different (17.2 ± 2.3 versus 17.2 ± 2.2; $p = 0.94$). Of the 260 DISC06 Follow-up Study participants, women who were pregnant or breastfeeding at the time of the visit or within 12 weeks before the visit (n=30) were not eligible for inclusion in the current analyses leaving a total of 230 women. Further, those who had breast implants or breast reduction surgery (n=16) were also not eligible for the inclusion in the analytic sample. Otherwise eligible women were excluded if they had a technically unacceptable MRI (n=21) or were missing MRI images (n=11). This resulted in an analytic sample of 182 participants. When compared with the analytic sample, there were no statistically significant differences in excluded participants that attended the DISC06 Follow-up visit with regards to age or BMI data collected at that visit.

Data collection

For the DISC06 Follow-up Study, each female participant attended a single data collection visit at one of the 6 DISC clinics between 2006 and 2008. Visits were scheduled to take place during the luteal phase of the menstrual cycle whenever possible and 85% took place within 14 days of the onset of the next menses. All data relevant to these analyses were collected on the same day. Data were collected by staff masked to treatment assignment. A centralized data collection training session was held prior to data collection to train and certify individuals responsible for this task.

Physical Activity—The historical version of the Modifiable Activity Questionnaire (MAQ) (22), an interviewer-administered recall questionnaire, was used to assess leisure-time physical activity levels during: (a) high school (ages 14–17 years), (b) post high school (ages 18–21 years) and (c) the previous 12 months (past year). The historical MAQ was adapted for use in the DISC06 Follow-up Study. For each time period, participants were asked to recall the frequency and duration of 55 common activities. Of these, six were domestic activities and were not included in the estimates of leisure-time physical activity. These lower intensity activities are also more difficult for individuals to recall and report accurately (21). For each time period (i.e., high school, post high school, and past year), total leisure-time physical activity was calculated as the product of the duration and frequency of the remaining leisure-time physical activities ($hr \cdot wk^{-1}$), weighted by a standardized estimate of the metabolic equivalent (MET) of each activity (1), and then summed for all activities performed. Summary estimates were also computed for leisure-time physical activity within specific intensity categories (i.e., light, moderate and vigorous). All physical activity estimates were expressed as metabolic equivalent hours per week ($MET \cdot hr \cdot wk^{-1}$). The MAQ, including the historical component, is a reliable and valid estimate of self-reported physical activity (22, 23, 33). Principal component analysis was used to reduce the three correlated physical activity estimates to a single principal component score representing total leisure-time physical activity across recall time periods. The first principal component, which represented the linear combination of the high school, post high school, and past year leisure-time physical activity estimates, explained 75.9% of the variance.

Breast Density—Breast density was measured using non-contrast MRI. Equipment standards were consistent with American College of Radiology (ACR) guidelines for breast MRI (2). Participants were imaged in a whole body 1.5 Tesla or higher field strength MRI scanner using a dedicated breast imaging radio-frequency coil. A standard image acquisition protocol was prescribed consisting of two pulse sequences performed in both the transaxial and coronal orientations with a 32 to 40 centimeter (cm) field of view for bilateral coverage: 3 dimensional (3D) fast gradient echo sequence: (a) without fat-saturation and (b) with fat-saturation.

To ensure accuracy and uniformity of data acquisition at the six different clinical centers, MRI technologists at the sites were individually trained to recognize and correct failures due to incomplete fat-suppression, motion artifacts, and inadequate breast coverage. In addition, acceptable image quality on three volunteers was required for site certification. Participant scans that were inaccurate due to artifacts, motion, or technique were excluded (n=21).

All MRI image data were processed at the University of California, San Francisco by the same study investigator (C. Klifa) using customized image processing software to: (a) identify the chest wall – breast tissue boundary and skin surface and (b) separate breast fibroglandular and fatty tissue using a segmentation method based on fuzzy C-means (FCM) clustering (20). FCM segmentation was performed using fat-suppressed images; non-fat suppressed images were used when incorrect or failed segmentation occurred due to poor fat-suppression. In problematic cases that could not be segmented with automated FCM methods, manual delineation was used. Total volumes of fibroglandular tissue (ADBV) and fatty tissue were computed separately for each breast and the average of the two values was used for analyses. %DBV was measured as the ratio of fibroglandular volume to total volume of the breast.

Anthropometric Measures—Height and body weight were measured with a stadiometer and electronic or beam balance beam scale, respectively. Each measurement was taken twice; a third measurement was taken if the first two measurements were not within allowable tolerances (i.e., 0.5 cm for height and 0.2 kg for weight) and the two closest values were averaged. BMI was computed as body weight in kg/(height in m)^2.

Other Covariates—DISC06 Follow-up study participants were asked to complete questionnaires to ascertain: (a) demographic characteristics, (b) medical, reproductive, and menstrual histories, (c) medication use, and (d) health behaviors including smoking and alcohol use. Race, educational attainment, smoking status, days until next menses, duration of hormonal contraceptive use, and parity were included as covariates for these analyses.

Statistical Methods

Descriptive analyses were conducted on all variables and their distributions were assessed. Normally distributed variables were reported as mean and standard deviation (SD), non-normal variables as median with interquartile range, and proportions were noted for categorical variables. Spearman rank order correlation coefficients were used to examine the bivariate association of physical activity levels for (a) high school, (b) post high school, (c) past year, and (d) principal component score with (e) childhood BMI (expressed as a z-score relative to CDC 2000 Growth Charts) measured at randomization (24) and (f) young adult BMI (kg/m^2) measured at the DISC06 Follow-up visit.

Leisure-time physical activity estimates were standardized to z-scores (mean = 0; SD = 1) relative to the observed distribution so that a unit change in each measure represents a change in one SD unit. %DBV and ADBV were transformed to natural logarithms. Generalized linear mixed (GLM) models were fit by residual maximum likelihood with random effects to examine the unadjusted and adjusted associations of total leisure-time physical activity estimates (listed as a-d above) with %DBV and ADBV, separately. Clinic was included in all models as a random effect; all other variables were entered as fixed effects. A three stage modeling strategy, including (a) variable specification, (b) interaction assessment, and (c) confounding assessment followed by consideration of precision was used to fit the models. Model 1 was the unadjusted model. Model 2 included terms for randomized treatment assignment in the original DISC Study, race (white or non-white), educational attainment (bachelor’s degree or less), smoking status (current or former/never), days until next menses (cubic spline), duration of hormonal contraceptive use, and number of full-term pregnancies (0 or ≥1). Model 3 included these terms plus childhood and young adult BMI. Due to a small variability among study participants, age (years) at the DISC06 Follow-up visit was not retained in the final multivariable adjusted models. Presence of interaction was evaluated by testing the significance of cross-product terms of variables in a model that also included their main effects. The presence of multicollinearity was evaluated by calculating the proportion of the variance from linear regression model. Percentage differences in %DBV and ADBV associated with a SD difference in (a) high school-, (b) post high school- and (c) past year- total leisure-time physical activity and (d) principal component score was estimated from models as $\Delta\% = (\exp(\beta) - 1) \times 100$. GLM models were repeated replacing total leisure-time physical activity estimates (listed as a-c above) with terms for both moderate- and vigorous- intensity physical activity at each time point. Analyses were repeated restricted to nulliparous women and separately with women not reporting hormonal contraceptives use at the DISC06 Follow-up visit. All statistical significance tests were two-sided. All statistical analyses were generated with SAS/STAT software, Version 9.3 (© 2002 – 2010) of the SAS System for Windows (Cary, NC).

Results

Participant characteristics are shown in Table 1. Participants included in the analytic sample were aged [mean ± SD] 27.2 ± 1.0 years and most were white (90.1%). The mean ± SD BMI was 25.3 ± 5.3 kg/m^2; with 18.1% being in the obese weight category. Most participants had a bachelor's or graduate degree (65.9%), were single (54.4%), and worked full-time (75.8%). A higher proportion were nulliparous (73.1%) compared to those reporting at least one full-term pregnancy. Further 57.7% and 36.3% reported either current or former hormonal contraceptive use at the DISC06 Follow-up visit, respectively. The mean ± SD duration of hormone use was 5.3 ± 3.7 years. Forty-four women (24.2%) reported current cigarette smoking use. The median (25th, 75th percentile) reported leisure-time physical activity was 34.7 (13.7, 66.6) MET·hr·wk^{-1} in high school, 30.9 (14.3, 54.3) MET·hr·wk^{-1} post high school, and 22.1 (9.3, 35.4) MET·hr·wk^{-1} during the previous 12 months. The median (25th, 75th percentile) %DBV was 24.5 (9.7, 41.2) and ADBV was 93.0 (50.0, 140.3) cubic centimeters (cm^3).

Neither high school (ages 14–17) nor post high school (ages 18–21) leisure time physical activity was statistically significantly associated with childhood or young adult BMI (data not shown). Past year leisure-time physical activity was significantly and inversely correlated with young adult BMI (rho = −0.24; p = 0.001). The correlation between current physical activity and childhood BMI (z-score) was not statistically significant. The principal component score, reflecting historical and current physical activity levels, was not statistically significantly related to either childhood or young adult BMI.

The associations of historical (i.e., high school and post high school) and current (i.e., past year) leisure-time physical activity with %DBV and ADBV after covariate adjustment are shown in Table 2. Reported physical activity during high school (ages 14–17 years) and post high school (ages 18–21 years) was not statistically significantly related to %DBV in multivariable models. In contrast, for every one SD increase in total past year leisure-time physical activity, %DBV increased by 21.6% (95% CI: 4.3, 41.8%; p=0.01) in Model 2. After additional adjustment for childhood and young adult BMI (Model 3), the association between past year leisure-time physical activity and %DBV was no longer statistically significant (p=0.15). However, in the fully adjusted model replacing past year total leisure physical activity with time-relevant intensity specific terms, every one SD increase in past year moderate intensity physical activity was associated with a %DBV increase of 13.8% (95% CI: 0.5, 28.8%; R^2 = 0.51; p=0.04); vigorous intensity physical activity was non-statistically significant. There were no other statistically significant associations between moderate- or vigorous-intensity estimates and %DBV or ABDV (data not shown). The principal component score, reflecting leisure-time physical activity across all time periods, was not statistically significantly related to %DBV. Further, the adjusted associations between self-reported leisure physical activity estimates and ADBV were not statistically significant.

The adjusted associations of historical and current leisure-time physical activity with %DBV and ADBV were repeated for participants reporting no current use of hormonal contraceptives at the DISC06 Follow-up visit (Table 3). Similar to models including the full analytic sample, high school (ages 14–17 years) and post high school (ages 18–21 years) leisure-time physical activity was not statistically significantly related to %DBV in multivariable models. In Model 2, each SD increase in past year leisure-time physical activity was associated significantly with approximately a 43.0% (95% CI: 2.9, 98.7%) increase in %DBV (p=0.03). After additional adjustment for BMI at baseline and DISC06 visit (Model 3), this association was no longer statistically significant. Leisure-time physical activity, recalled from any time point, was not statistically significantly related to ADBV after covariate adjustment. Among nulliparous women, physical activity at any time point was not statistically significantly associated with %DBV or ADBV (data not shown).

Discussion

The current study extends previous research in the area of physical activity and breast density by examining this association in women from adolescence to early adulthood. After adjustment for important covariates, results showed that higher levels of current (i.e., past year) leisure-time physical activity levels were significantly, yet directly, related to %DBV, but not ADBV among women aged 25–29 years. Following further adjustment for childhood and young adult BMI, the relationship between current leisure-time physical activity and %DBV was no longer statistically significant. No statistically significant associations were found between historical (high school and post high school) leisure-time physical activity levels and %DBV or ADBV. Results were similar when associations with breast density measures were examined using physical activity data that were collected prospectively in the original DISC Study (data not shown). Given the null associations between high school and post high school physical activity and breast density outcome measures, we are unable to confirm our initial hypothesis. However, these findings are consistent with earlier studies showing a null association between physical activity and breast density in older women (39).

Previous studies in the area of physical activity and breast density have primarily targeted midlife to older women (39); however, the current study population consisted of younger, premenopausal women in their mid- to late- twenties. Given our intention to examine the influence of adolescent and early adulthood physical activity levels on measures of breast density, the use of a younger sample population eliminated the necessity for a lengthy exposure recall that was required of previous studies. To our knowledge, five previous studies (19, 30, 34–36) have examined the role of early-life exposures on adult breast density (39). However, unlike the current study, breast density was ascertained via mammography. Further, study participants for these studies were much older than DISC06 Study participants with most study populations having a mean or median age of 50 years and older (19, 30, 34, 36), which substantially lengthened the physical activity recall period. Regardless, similar to our findings, physical activity during early life was not significantly associated with mammographically defined percent dense breast area (%DBA) in any of these previous studies (19, 30, 34–36).

The positive association that was found between current leisure-time physical activity and %DBV (Models 1 and 2) is consistent with the results of a previous investigation by Irwin and colleagues (17). In the Irwin study (17), the relations between physical activity levels and %DBA and absolute dense breast area (ADBA) retrieved from mammograms one year prior to diagnosis were examined in women with breast cancer. At the baseline visit, participants recalled physical activity levels during the year prior to breast cancer diagnosis using an adapted version of the MAQ and the associations between physical activity and breast composition measures were examined separately by menopausal- (pre- and post-menopause) and obesity- (BMI < 30 kg/m^2 and BMI ≥ 30 kg/m^2) status. Among premenopausal women, %DBA and ADBA were greater in non-obese women when compared to obese women. Further, among non-obese, premenopausal women, %DBA was statistically significantly higher across increasing physical activity (sports/recreation) categories that were based on the physical activity recommendations available at the time of the study (28) (p for trend = 0.037) (17). However, the linear association with ADBA was not statistically significant. In obese, premenopausal women the relations of physical activity with %DBA and ADBA were also not statistically significant.

Findings from the study by Irwin and colleagues (17) suggest that obesity status may modify the association between physical activity and breast composition in premenopausal women. Physically active individuals tend to have a lower BMI when compared to less active counterparts (3); an inverse association that was also demonstrated in the current study. The parenchymal pattern of the female breast can vary from completely fatty to extremely dense (29). Intuitively, with increases in adiposity, total breast area should increase due to increased fat while the absolute area of dense tissue remains the same. In a recent study of DISC participants by Dorgan and colleagues, BMI measured at the DISC06 Follow-up visit predicted 49% of the variability in %DBV, but only 7% of the variability in ADBV (11). After adjustment for clinic site, race, education, smoking status, duration of hormone use, and parity, adult BMI remained significantly, inversely related to both %DBV and ADBV (11). In the current analysis, interaction terms between leisure-time physical activity estimates and BMI, used both as a continuous and categorical (<30 or ≥ 30 kg/m^2) variable, were tested in each of the models; however, none were statistically significant. The non-statistically significant interactions are likely the reflection of the low proportion (18.1%) of the analytic sample that was classified as obese. Future studies should examine the role of obesity as an effect modifier in the association between physical activity and %DBV and ADBV in younger, premenopausal women with no previous diagnosis of breast cancer.

Mammography is not a recommended screening tool for breast cancer in young women due to the associated radiation exposure (4). Further, mammography has been shown to be less sensitive to detect breast cancer in women aged 40 years and younger (32). Together, these factors contribute to the lack of published literature related to breast density in this age group. MRI has been shown to be highly correlated (r= 0.79) with mammographic density (16), but avoids the radiation exposure associated with mammography. Therefore, this study contributes significantly to the literature by exploring the relation between physical activity and breast density using MRI in young, adult women. Other important strengths of this study include: (a) data were collected on the majority of participants (79.1%) during the luteal phase of the menstrual cycle, (b) availability of physical activity data spanning from adolescence to early adulthood, and (c) ability to conduct sub-analyses in in nulliparous women and participants reporting no hormonal contraceptive use at the DISC06 Follow-up visit.

In addition to strengths, there are also limitations to consider when interpreting these results. First, women included in the current investigation were specifically recruited during childhood for a dietary intervention that specifically targeted a reduction in LDL-C levels. However, only 14 (7.8%) participants included in the analyses had high LDL-C levels at follow-up visits based on National Cholesterol Education Program guidelines (27), and none were using cholesterol lowering medications. Even so, DISC06 Follow-up study participants may not be representative of the general population. Second, the relatively small sample size reduced statistical power, which could have resulted in a type II error. Third, historical and current physical activity levels were self-reported, which has several drawbacks including recall error and incomplete ascertainment of the exposure across multiple domains and intensity levels (21, 38). Future research in this area should incorporate device-based measures (e.g., accelerometers) into their measurement strategy to clarify the importance of specific physical activity characteristics (i.e., total amount versus intensity level) on breast health in younger women. Nonetheless, in the current study, physical activity estimates were obtained from a widely implemented quantitative historical questionnaire with established test-retest reliability and convergent validity when compared to the Paffenbarger (i.e., College Alumnus) Physical Activity Questionnaire and activity monitor (22, 23). Further, participants did not have access to their breast density data at the time physical activity was assessed, which also limits the possibility of recall bias. Again, an important strength of this study was that physical activity exposures were recalled over much shorter time periods when compared to previous studies in this area (14). This likely improved the precision and accuracy of the self-reported estimates to compare with the breast density measures. Further, as mentioned previously, similar results were obtained using prospective physical activity data collected in DISC.

The current study adds to previous research by exploring the role of physical activity during critical periods of breast development in relation to MRI determined measures of breast density in younger women. Although the relations of physical activity during high school and post high school with %DBV and ADBV were not statistically significant, reported physical activity during the previous 12 months was shown to be directly related to %DBV in Model 1 and 2. After additional adjustment for childhood and young adult BMI (Model 3); however, this association was no longer statistically significant. Consistent with previous research (39), the findings from the current study suggest that physical activity at a young age is unrelated to breast density.

Acknowledgments

Funding Sources: American Institute for Cancer Research (10A093 to K.P.G.) and National Cancer Institute (R01CA104670 to J.F.D.).

We thank all of the DISC06 participants. This research was funded by the American Institute for Cancer Research (10A093 to K.P.G.) and National Cancer Institute (R01CA104670 to J.F.D.).

References

1. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: A Second Update of Codes and MET Values. Med Sci Sports Exerc. 2011; 43(8):1575–81. [PubMed: 21681120]
2. American College of Radiology Website [Intranet]. ACR practice guideline for the performance of contrast-enhanced magnetic resonance imaging (MRI) of the breast. 2008. [cited 2012 October 11]
3. Blair SN, LaMonte MJ, Nichaman MZ. The evolution of physical activity recommendations: how much is enough? Am J Clin Nutr. 2004; 79(5):913S–20S. [PubMed: 15113739]
4. Boyd N, Martin L, Chavez S, Gunasekara A, Salleh A, Melnichouk O, Yaffe M, Friedenreich C, Minkin S, Bronskill M. Breast-tissue composition and other risk factors for breast cancer in young women: a cross-sectional study. Lancet Oncol. 2009; 10(6):569–80. [PubMed: 19409844]
5. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 1998; 7(12):1133–44. [PubMed: 9865433]
6. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Res. 2011; 13:223. [PubMed: 22114898]
7. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol. 2005; 6(10):798–808. [PubMed: 16198986]
8. Conroy SM, Butler LM, Harvey D, Gold EB, Sternfeld B, Oestreicher N, Greendale GA, Habel LA. Physical activity and change in mammographic density: the Study of Women's Health Across the Nation. Am J Epidemiol. 2010; 171(9):960–8. [PubMed: 20354074]
9. DISC Collaborative Research Group. Dietary intervention study in children (DISC) with elevated low-density-lipoprotein cholesterol. Design and baseline characteristics. DISC Collaborative Research Group. Ann Epidemiol. 1993; 3(4):393–402. [PubMed: 8275216]

10. DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). JAMA. 1995; 273(18):1429–35. [PubMed: 7723156]
11. Dorgan JF, Klifa C, Shepherd JA, Egleston BL, Kwiterovich PO, Himes JH, Pettee Gabriel K, Van Horn L, Snetselaar LG, Stevens VJ, Barton BA, Robson AM, Lasser NL, Deshmukh S, Hylton NM. Height, adiposity and body fat distribution and breast density in young women. Breast Cancer Res. 2012; 14:R107. [PubMed: 22800711]
12. Dorgan JF, Liu L, Klifa C, Hylton N, Shepherd JA, Stanczyk FZ, Snetselaar LG, Van Horn L, Stevens VJ, Robson A, Kwiterovich PO Jr, Lasser NL, Himes JH, Pettee Gabriel K, Kriska A, Ruder EH, Fang CY, Barton BA. Adolescent diet and subsequent serum hormones, breast density, and bone mineral density in young women: results of the Dietary Intervention Study in Children follow-up study. Cancer Epidemiol Biomarkers Prev. 2010; 19(6):1545–56. [PubMed: 20501774]
13. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from two case-control studies. Cancer Epidemiol Biomarkers Prev. 2000; 9(7):681–7. [PubMed: 10919738]
14. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med. 2008; 42(8):636–47. [PubMed: 18487249]
15. Garland M, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Spiegelman D, Speizer F, Willett WC. Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. Am J Epidemiol. 1998; 147(7):636–43. [PubMed: 9554602]
16. Graham SJ, Bronskill MJ, Byng JW, Yaffe MJ, Boyd NF. Quantitative correlation of breast tissue parameters using magnetic resonance and X-ray mammography. Br J Cancer. 1996; 73(2):162–8. [PubMed: 8546901]
17. Irwin ML, Aiello EJ, McTiernan A, Baumgartner RN, Baumgartner KB, Bernstein L, Gilliland FD, Ballard-Barbash R. Pre-diagnosis physical activity and mammographic density in breast cancer survivors. Breast Cancer Res Treat. 2006; 95(2):171–8. [PubMed: 16319988]
18. Irwin ML, Aiello EJ, McTiernan A, Bernstein L, Gilliland FD, Baumgartner RN, Baumgartner KB, Ballard-Barbash R. Physical activity, body mass index, and mammographic density in postmenopausal breast cancer survivors. J Clin Oncol. 2007; 25(9):1061–6. [PubMed: 17261853]
19. Jeffreys M, Warren R, Gunnell D, McCarron P, Smith GD. Life course breast cancer risk factors and adult breast density (United Kingdom). Cancer Causes Control. 2004; 15(9):947–55. [PubMed: 15577297]
20. Klifa C, Carballido-Gamio J, Wilmes L, Laprie A, Lobo C, Demicco E, Watkins M, Shepherd J, Gibbs J, Hylton N. Quantification of breast tissue index from MR data using fuzzy clustering. Conf Proc IEEE Eng Med Biol Soc. 2004; 3:1667–70. [PubMed: 17272023]
21. Kriska AM, Caspersen CJ. Introduction to a Collection of Physical Activity Questionnaires. Med Sci Sports Exerc. 1997; 29(6):S5–S9.
22. Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, Bennett PH, Kuller LH. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. Diabetes Care. 1990; 13(4):401–11. [PubMed: 2318100]
23. Kriska AM, Sandler RB, Cauley JA, LaPorte RE, Hom DL, Pambianco G. The assessment of historical physical activity and its relation to adult bone parameters. Am J Epidemiol. 1988; 127(5):1053–63. [PubMed: 3358406]
24. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat. 2002; 11(246):1–190.
25. Marmara EA, Papacharalambous XN, Kouloulias VE, Maridaki DM, Baltopoulos JP. Physical activity and mammographic parenchymal patterns among Greek postmenopausal women. Maturitas. 2011; 69(1):74–80. [PubMed: 21377300]
26. Martin LJ, Boyd NF. Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. Breast Cancer Res. 2008; 10:201. [PubMed: 18226174]

27. National Cholesterol Education Program. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285(19):2486–97. [PubMed: 11368702]

28. Pate RR, Pratt M, Blair SN, Haskell WL, Macera CA, Bouchard C, Buchner D, Ettinger W, Heath GW, King AC, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995; 273(5):402–7. [PubMed: 7823386]

29. Porter GJ, Evans AJ, Cornford EJ, Burrell HC, James JJ, Lee AH, Chakrabarti J. Influence of mammographic parenchymal pattern in screening-detected and interval invasive breast cancers on pathologic features, mammographic features, and patient survival. AJR Am J Roentgenol. 2007; 188(3):676–83. [PubMed: 17312053]

30. Reeves KW, Gierach GL, Modugno F. Recreational physical activity and mammographic breast density characteristics. Cancer Epidemiol Biomarkers Prev. 2007; 16(5):934–42. [PubMed: 17507619]

31. Samimi G, Colditz GA, Baer HJ, Tamimi RM. Measures of energy balance and mammographic density in the Nurses' Health Study. Breast Cancer Res Treat. 2008; 109(1):113–22. [PubMed: 17592770]

32. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, Morris E, Pisano E, Schnall M, Sener S, Smith RA, Warner E, Yaffe M, Andrews KS, Russell CA. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007; 57(2):75–89. [PubMed: 17392385]

33. Schulz LOHI, Smith CJ, Kriska AM, Ravussin E. Energy intake and physical activity in Pima Indians: comparison with energy expenditure measured by doubly-labeled water. Obes Res. 1994; 2:541–8. [PubMed: 16355515]

34. Sellers TA, Vachon CM, Pankratz VS, Janney CA, Fredericksen Z, Brandt KR, Huang Y, Couch FJ, Kushi LH, Cerhan JR. Association of childhood and adolescent anthropometric factors, physical activity, and diet with adult mammographic breast density. Am J Epidemiol. 2007; 166(4):456–64. [PubMed: 17548785]

35. Siozon CC, Ma H, Hilsen M, Bernstein L, Ursin G. The association between recreational physical activity and mammographic density. Int J Cancer. 2006; 119(7):1695–1701. [PubMed: 16688715]

36. Tseng M, Olufade TO, Evers KA, Byrne C. Adolescent lifestyle factors and adult breast density in U.S. Chinese immigrant women. Nutr Cancer. 2011; 63(3):342–9. [PubMed: 21391125]

37. Warren MP, Perlroth NE. The effects of intense exercise on the female reproductive system. J Endocrinol. 2001; 170(1):3–11. [PubMed: 11431132]

38. Westerterp KR. Assessment of physical activity: a critical appraisal. Eur J Appl Physiol. 2009; 105(6):823–8. [PubMed: 19205725]

39. Yaghjyan L, Colditz GA, Wolin K. Physical activity and mammographic breast density: a systematic review. Breast Cancer Res Treat. 2012; 135(2):367–80. [PubMed: 22814722]

Table 1

Characteristics of Dietary Intervention Study in Children (DISC) participants at the DISC06 visit.

	n	Analytic Sample[a]
Participant Characteristics		
Collected at Baseline		
Age at Randomization, years	182	9.2 ± 0.6
BMI at Randomization, Z-score	182	0.2 ± 0.9
BMI at Randomization, kg/m^2	182	17.3 ± 2.3
Overweight (above 95th percentile of BMI for sex and age), %	10	5.5
Collected at DISC06 Visit		
Age at Visit, years	182	27.2 ± 1.0
Race		
White, %	164	90.1
Black, %	11	6.0
Other, %	7	3.9
Educational Attainment		
< Bachelor’s Degree, %	62	34.1
≥ Bachelor’s Degree, %	120	65.9
Anthropometric Measures		
Height, cm	182	165.3 ± 6.4
Weight, kg	182	69.3 ± 15.4
Body Mass Index (BMI) at Visit, kg/m^2	182	25.3 ± 5.3
Reproductive History		
Age at Onset of Menstruation, years	182	12.9 ± 1.3
Menstrual Cycle Phase at Visit		
Luteal (1–14 d before menses), %	144	79.1
Follicular (15–34 d before or on day of menses), %	18	9.9
Long cycle (35+ d before menses), %	7	3.9
Missing, %	13	7.1
Next Menses, days	169	6.0 (4.0. 9.0)
Current Hormonal Contraceptive Use		
Never, %	11	6.0
Former, %	66	36.3
Current, %	105	57.7
Duration of Hormone Use, years	182	5.3 ± 3.7
Full Term Pregnancy		
None, %	133	73.1
≥ 1, %	49	26.9
Behavioral Characteristics		

	n	**Analytic Sample**[a]
Smoking Status, %		
Never, %	100	54.9
Former, %	38	20.9
Current, %	44	24.2
Total Leisure-time Physical Activity (PA) at 14–17 years, MET·hr·wk^{-1}	182	34.7 (13.7, 66.6)
Light Intensity Leisure-time PA at 14–17 years, MET·hr·wk^{-1}		0.0 (0.0, 0.3)
Moderate Intensity Leisure-time PA at 14–17 years, MET·hr·wk^{-1}		11.7 (5.2, 29.4)
Vigorous Intensity Leisure-time PA at 14–17 years, MET·hr·wk^{-1}		17.5 (3.2, 39.5)
Total Leisure-time PA at 18–21 years, MET·hr·wk^{-1}	182	30.9 (14.3, 54.3)
Light Intensity Leisure-time PA at 18–21 years, MET·hr·wk^{-1}		0.0 (0.0, 0.2)
Moderate Intensity Leisure-time PA at 18–21 years, MET·hr·wk^{-1}		15.2 (5.9, 33.2)
Vigorous Intensity Leisure-time PA at 18–21 years, MET·hr·wk^{-1}		11.1 (4.3, 23.2)
Total Past Year Leisure-time PA, MET·hr·wk^{-1}	182	22.1 (9.3, 35.4)
Past Year Light Intensity PA, MET·hr·wk^{-1}		0.0 (0.0, 0.1)
Past Year Moderate Intensity PA, MET·hr·wk^{-1}		10.9 (4.7, 22.8)
Past Year Vigorous Intensity PA, MET·hr·wk^{-1}		6.3 (1.6, 14.5)
Breast Composition Measures		
Percent dense breast volume (%DBV)	182	24.5 (9.7, 41.2)
Absolute dense breast volume (ADBV), cm^3	182	93.0 (50.0,140.3)

[a] Normally-distributed variables presented as mean ± standard deviation; non-normal variables presented as median (interquartile range); categorical variables presented as proportions.

Table 2

Percentage difference in percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) associated with a one standard deviation difference in adolescent and young adulthood leisure-time physical activity.

	MODEL 1 Unadjusted[a]					MODEL 2 Adjusted[b]					MODEL 3 Also adjusted for childhood and young adult BMI[c]				
Percent Dense Breast Volume (%DBV)															
Leisure time Physical Activity Estimate, MET·hr·wk^{-1}	**n**	**% Diff**	**95% CI**	**p**	**R^2[d]**	**n**	**% Diff**	**95% CI**	**p**	**R^2[d]**	**n**	**% Diff**	**95% CI**	**p**	**R^2[d]**
High School (14–17 years)	180	6.4	−8.8, 24.1	0.43	0.01	167	1.3	−14.0, 19.2	0.88	0.07	167	3.2	−8.2, 16.0	0.60	0.52
Post High School (18–21 years)	182	9.9	−5.6, 28.1	0.22	0.03	169	2.7	−12.4, 20.3	0.74	0.06	169	0.5	−10.3, 12.7	0.93	0.52
Past Year	182	30.7	12.8, 51.5	<0.001	0.06	169	21.6	4.3, 41.8	0.01	0.10	169	8.7	−3.0, 21.7	0.15	0.52
Principal Component Score[e]	180	10.9	−4.8, 29.2	0.18	0.02	167	3.4	−12.1, 21.6	0.68	0.07	167	2.4	−8.9, 15.0	0.69	0.52
Absolute Dense Breast Volume (ADBV)															
High School (14–17 years)	180	4.9	−7.7, 19.2	0.46	0.0	167	1.5	−11.2, 16.1	0.83	0.08	167	1.0	−10.8, 14.5	0.87	0.20
Post High School (18–21 years)	182	−0.22	−12.1, 13.2	0.97	0.0	169	−4.0	−15.6, 9.2	0.53	0.08	167	−3.9	−14.8, 8.4	0.51	0.20
Past Year	182	10.2	−2.7, 24.9	0.12	0.01	169	4.9	−7.6, 19.1	0.46	0.08	169	2.5	−9.1, 15.7	0.68	0.20
Principal Component Score[e]	180	4.3	−8.1, 18.4	0.51	0.0	167	−0.3	−12.7, 13.8	0.96	0.08	167	−1.2	−12.7, 11.9	0.85	0.20

[a] Estimates from four linear mixed effects models for each outcome (%DBV and ADBV) including clinic site as a random effect and leisure time physical activity estimates as fixed effects. Adolescent and young adulthood leisure time physical activity estimates are modeled separately without mutual adjustment.

[b] Estimates from four linear mixed effects models as described above under 'a' plus including treatment group, race [white (0) or. non-white (1)], education [did not attend (0) or. attended (1) 4 year college], smoking status [former/never (0) or current (1)], days until next menses (cubic spline), duration of oral contraceptive use, and parity [none (0) or ≥1 (1)] as fixed effects.

[c] Estimates from four linear mixed effects models as described above under 'b' plus including BMI z-score at 8–10 years old and adult BMI.

[d] Proportion of variance explained by model.

[e] Principal component score includes high school, post high school, and past year leisure time physical activity estimates.

Table 3

Percentage difference in percent dense breast volume (%DBV) and absolute dense breast volume (ADBV) associated with a one standard deviation difference in adolescent and young adulthood leisure-time physical activity in current non-oral contraceptive users only.

	MODEL 1 Unadjusted[a]					MODEL 2 Adjusted[b]					MODEL 3 Also adjusted for childhood and young adult BMI[c]				
Percent Dense Breast Volume (%DBV)															
Leisure time Physical Activity Estimate, MET·hr·wk^{-1}	**n**	**% Diff**	**95% CI**	**p**	**R^{2d}**	**n**	**% Diff**	**95% CI**	**p**	**R^{2d}**	**n**	**% Diff**	**95% CI**	**p**	**R^{2d}**
High School (14–17 years)	76	3.2	−17.9, 29.6	0.79	0.02	74	−3.8	−23.1, 20.4	0.73	0.19	74	2.9	−13.1, 21.9	0.74	0.55
Post High School (18–21 years)	77	15.9	−10.2, 49.6	0.25	0.01	75	5.8	−18.3, 37.1	0.66	0.13	75	−1.4	−18.5, 19.4	0.89	0.55
Past Year	77	51.7	15.4, 99.4	0.003	0.11	75	43.0	2.9, 98.7	0.03	0.20	75	13.6	−12.5, 47.4	0.33	0.55
Principal Component Score[e]	76	9.8	−13.0, 38.6	0.43	0.03	74	0.4	−20.3, 26.4	0.97	0.19	74	2.2	−14.1, 21.6	0.80	0.55
Absolute Dense Breast Volume (ADBV)															
High School (14–17 years)	76	3.2	−13.0, 22.3	0.71	0.00	74	−0.2	−15.2, 17.4	0.98	0.16	74	−0.3	−15.1, 17.2	0.98	0.18
Post High School (18–21 years)	77	3.5	−14.3, 25.2	0.72	0.00	75	−2.4	−19.0, 17.6	0.80	0.14	75	−3.5	−19.6, 15.9	0.70	0.18
Past Year	77	10.9	−10.3, 37.1	0.33	0.00	75	8.3	−15.6, 39.0	0.52	0.14	75	2.6	−20.2, 31.9	0.84	0.17
Principal Component Score[e]	76	4.0	−12.6, 23.8	0.65	0.00	74	−0.5	−16.0, 17.7	0.95	0.16	74	−1.1	−16.3, 16.9	0.90	0.18

[a] Estimates from four linear mixed effects models for each outcome (%DBV and ADBV) including clinic site as a random effect and leisure time physical activity estimates as fixed effects. Adolescent and young adulthood leisure time physical activity estimates are modeled separately without mutual adjustment.

[b] Estimates from four linear mixed effects models as described above under ‘a’ plus including treatment group, race [white (0) or. non-white (1)], education [did not attend (0) or. attended (1) 4 year college], smoking status [former/never (0) or current (1)], days until next menses (cubic spline), duration of oral contraceptive use, and parity [none (0) or ≥1 (1)] as fixed effects.

[c] Estimates from four linear mixed effects models as described above under ‘b’ plus including BMI z-score at 8–10 years old and adult BMI.

[d] Proportion of variance explained by model.

[e] Principal component score includes high school, post high school, and past year leisure time physical activity estimates.