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Adolescent Physical Activity and Inactivity: A Prospective Study of Risk of Benign Breast Disease in Young Women

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Abstract

Purpose—In previous investigations of adolescent activity recalled in adulthood, modest reductions in risk of benign breast disease (BBD) and premenopausal breast cancer were seen with moderate-strenuous activity during high school. We therefore investigated physical activity, walking, and recreational inactivity (watching TV-videos, playing computer-videogames) reported by adolescent girls in relation to their subsequent risk for BBD as young women.

Methods—The Growing Up Today Study (GUTS) includes 9039 females, 9–15yrs at study initiation (1996), who completed questionnaires annually through 2001, then 2003, 2005, 2007, 2010 and 2013. Annual surveys (1996–2001) obtained data on physical and sedentary activities during the past year. Beginning in 2005, women (≥18yr) reported whether they had been diagnosed with BBD confirmed by breast biopsy (n=133 cases, to 11/01/2013). Logistic regression (adjusted for baseline adiposity and age; additional factors in multivariable-adjusted models) estimated associations between adolescent activities (moderate-vigorous, walking, METS, inactivity) and biopsy-confirmed BBD in young women.

Results—Girls who walked the most had significantly lower risk of BBD (multivariable-adjusted OR=0.61, p=.049, 30min/day vs 15min/day). We observed no evidence that inactivity (≥3 hrs/day vs <2hr/day OR=1.02, p=.92) or METS (top vs bottom tertile OR=1.19, p=.42) were associated with BBD.

Conclusion—Accounting for factors including family history, childhood adiposity, other activities and inactivities, adolescent girls who walked the most were at lower risk for BBD. We found no evidence that high moderate-vigorous activity might reduce risk, nor did we observe any

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Conflict of Interest

The authors declare that they have no conflict of interest.

association with inactivity. Continued follow-up will re-evaluate these findings as more BBD cases, and ultimately breast cancer, are diagnosed.

Keywords

adolescence; moderate-vigorous activity; walking; inactivity; sleep; BBD

Introduction

Substantial evidence implicates the period in life before a woman's initial pregnancy, when mammary gland cells are undergoing rapid proliferation, as a critical time for carcinogenic exposures that may increase her lifetime risk for breast cancer [1]. Certain childhood and adolescent exposures have been shown to be more important than adult exposures in breast cancer development [2–5], so prevention efforts must begin early [6]. Investigations of lifetime physical activity found significantly reduced risk for premenopausal breast cancer among women with high levels of regular exercise from menarche into adulthood, providing a risk factor that can be personally altered [7–8].

Because benign breast disease (BBD) is a well-established risk factor for breast cancer [9], the investigation of exposures in girls and their subsequent development of BBD may provide insight into the etiology of breast cancer and present possible new strategies for prevention. We previously reported that adolescent alcohol consumption (recorded prospectively) was associated with increased risk of BBD in young women [10], while adolescent intake of vegetable protein was associated with reduced risk [11]. Other authors, using adolescent activity data recalled by adult women, found that strenuous physical activity during high school, for 4–9 months of the year, was associated with lower risk for proliferative BBD [12], but no association was seen for activity during ages 18–22yr.

To overcome concerns regarding the accuracy of adult recall of adolescent behaviors, we investigated whether prospectively reported adolescent moderate-vigorous physical activity was associated with subsequent BBD in young women. We further investigated walking and recreational inactivity (watching TV or videos, playing video-computer games), adolescent factors not previously considered in the study of BBD. Our data come from a cohort of children that was initiated in 1996, including females aged 9–15yr at the time, with ongoing follow-up.

Materials and Methods

Study Population

The Growing Up Today Study (GUTS; founding PI, Dr. Colditz) includes 9039 girls from all 50 states who are daughters of Nurses' Health Study II (NHSII) participants [13]. The study, approved by Institutional Review Boards at Harvard School of Public Health and Brigham and Women's Hospital, is described elsewhere [14]. Mothers provided informed consent, and their 9–15 yr old daughters assented by completing baseline questionnaires. The cohort returned questionnaires annually (by mail or Internet) from 1996 through 2001, then in 2003, 2005, 2007, 2010 and 2013. The response rate to one or more follow-ups after

baseline was 97%. Over 80% returned at least one of the 2005 or later surveys inquiring about BBD.

Benign Breast Disease

The 2005, 2007, 2010 and 2013 surveys inquired “Has a health care provider ever diagnosed you as having Benign Breast Disease?” and, if yes, whether it had been “Confirmed by breast biopsy”. A total of 7222 females (aged 18+yr) reported whether a health care provider ever, or never, diagnosed them with BBD (n=315 said yes), and if any diagnosis had been confirmed by breast biopsy (n=133). After excluding six girls whose mothers reported childhood cancer in their daughters, 6901 females who returned surveys during this period but never reported a BBD diagnosis provide the non-cases for these analyses.

Most BBD cases were likely diagnosed because participants (or their physicians) found a clinically palpable mass which was then biopsied, for participants were too young to be undergoing routine screening mammography. The most common type of BBD occurring in adolescents and young women is fibroadenoma, which accounts for nearly 70% of benign breast lesions [15]. The remaining types are primarily cysts and fibrocystic changes [15]. A validation study conducted in NHSII women confirmed the accuracy of self-reports of biopsy-confirmed BBD [16].

Physical Activity

We developed a physical activity questionnaire for youth that asked them to recall the typical number of hours per week, over the past year, in various activities and team sports. This questionnaire was administered annually, 1996–2001. Questions included, separately for 17 sports and other activities (like hard work outdoors, biking, walking), how many hours/week they typically engaged in them. From 16 of these activities (walking omitted), we computed total hours of moderate and vigorous physical activity per week, separately for each survey year; estimates exceeding 40hrs/wk were excluded as unreliable (1.3%). We were unable to ascertain details of varying intensity (within sport), or duration per session of activity. However, we did assign a metabolic equivalent (MET), obtained from Ainsworth's compendium of physical activities [17], to individual sports and activities. This allowed us to estimate total METs per week (walking included) for each girl, for each year. Assessments of our physical activity instrument found that estimates of total activity were moderately reproducible ($r=0.49$ for girls) and reasonably correlated with cardio-respiratory fitness, providing evidence of validity [18]. Another validation study reported a correlation of $r=0.80$ between survey self-reports and 24-hr recalls [19]. Validity is also supported implicitly by our earlier investigations; statistically significant inverse associations were found between physical activity (and increasing activity over time) and change in BMI [14,20].

Inactivity

Another series of questions on annual surveys (1996–2001) measured recreational sedentary behaviors. For watching television-videos and playing video-computer games, children reported their typical time doing these activities, from which we derived each girl's total hrs/wk of recreational inactivity (for each survey year); estimates exceeding 80hrs/wk were excluded as unreliable (0.3%). Moderate validity was reported for recalled inactivity from a

similar instrument [19]. Earlier work [14,20] found significant positive associations between these measures of recreational inactivity and increase over time in BMI in these girls.

Two of our surveys (1999, 2001) asked about hours of sleep on nights before school or work. We previously reported that girls getting less sleep had larger year-to-year increases in BMI [21].

Other Variables

At baseline, participants reported their race/ethnic group by marking all (of six) options that applied to them; most are white/non-Hispanic (95%), as are BBD cases. We computed ages (to the month) from dates of questionnaire return and birth. Early surveys annually asked “Have you started having menstrual periods?” and “If yes, age when periods began”. Childhood adiposity at age 10yr was derived from baseline body mass index (BMI, kg/m²) [22]. Multiple surveys asked females whether they had been pregnant. Adolescent alcohol intake was obtained from alcohol consumption reported on the 2000–2003 surveys [10]. Derivation of vegetable protein intakes, and peanut butter and nuts, is described elsewhere [11]. Participants’ family history of breast disease was provided by their mothers [23].

Statistical Analyses

To assess potential for selection bias, using baseline data we compared participants who returned year 2005 or later surveys including BBD questions with those who did not.

Risk of biopsy-confirmed BBD was the outcome for all analyses. Logistic regression models, estimated using SAS [24], provided odds ratios (OR) and 95% confidence intervals (CI). Because baseline age was related to being diagnosed during follow-up, all models adjusted for baseline age (to month). Considerable evidence supports childhood adiposity, as early as 5yr, being strongly protective against breast cancer [5,12,25] and BBD [12,22], so all models further adjusted for childhood adiposity. Multivariable-adjusted models additionally included age at menarche, family history of breast disease, adolescent alcohol intake, energy-adjusted vegetable protein intake or peanut butter and nuts, and ever pregnant (yes, no). They also included together physical activity and inactivity variables, for mutual adjustment.

Exposure variables that we analyzed were moderate-vigorous physical activity (hrs/day), walking (hrs/day), METS/day, and recreational inactivity (hrs/day). We focused on exposures occurring at age 14yr (typically the first year of high school) because 14yr falls within the biologically critical period between menses-onset and first pregnancy, and physical activity in high school affects menstrual cycle patterns and ovulatory frequency [26]. Furthermore, all girls in our cohort were 14yr sometime during follow-up (1996–2001) when we collected data on these exposures, so due to our GUTS study design this is the best exposure to investigate. (Girls age 9 at baseline were 14yr in 2001, the last year these exposures were collected, while the oldest girls were 14yr at baseline, and the remainder were 14yr sometime between 1996 and 2001.) Girls of this age should be able to more validly report (than when younger) their activities. When exposure data were unavailable for a particular girl exactly at age 14, values between ages 13.5 and 15.5yrs were sought, and if still missing, values were obtained between ages 13.0 and 15.99 yr. Models were fit using

continuous measures of exposures (hours/day or METS/day), but models were also fit using 3-level categorical versions of each factor, to consider nonlinear associations.

Finally, because we currently have a larger number of biopsy-confirmed BBD cases (N=133) than when we published our earlier work (our initial BBD paper included 67 cases [10]), we present newly estimated associations between our previously investigated risk factors and BBD. Aside from the larger number of cases, the multivariable-adjusted models now (for the first time) adjust for physical activity and inactivity.

Results

Eighty percent of our cohort returned, between 2005 and November 1, 2013, at least one survey containing questions about BBD. Comparing baseline data of these females with the 20% returning none of those surveys, we found only very small differences with respect to the exposures evaluated in this study. For example, the included girls were slightly younger (by 5.6 weeks) than those not included, were less physically active (−6.5 minutes/day), less inactive (−15 minutes/day), and spent less time walking (−2 minutes/day) (each age-adjusted $p < .05$). However, baseline BMI, energy intake, and menarche status were each similar for the included and missing females. These small differences are unlikely to present serious sources of bias.

Table 1 provides means (or percents), within tertile of METS at age 14yr, of each activity variable along with other important characteristics. As expected, the physical activity variables (moderate-vigorous activity, walking) had larger means in higher MET tertiles, but inactivity did not vary by tertile of METS, whereas sleep tended to decline slightly with more METS. Surprisingly, the most biopsy-confirmed BBD cases (2.3%) were among girls in the most active METS tertile. The most active girls also tended to have more mothers with BBD (19.8%), but they also had fewer mothers with breast cancer (6.8%) than less active girls.

Table 2 summarizes the results from our analyses, where for each physical activity and inactivity variable, we present four odds ratios: two from their analyses as continuous measures (age-BMI-adjusted, or multivariable-adjusted) and two from their analyses as categorical variables (age-BMI-adjusted, or multivariable-adjusted) showing the odds ratio of the highest relative to lowest exposure group. Walking at age 14yr was associated with lower risk for BBD (multivariable-adjusted OR=0.61 for 30minutes/day relative to 15 minutes/day, $p=.049$). Though these girls were quite physically activity, they spent little time walking: 64% were in the referent group (15 minutes/day) while only 22% walked 30minutes/day, but benefit was suggested even for the 13% who walked between 15 and 30min/day (OR=0.78, $p=.37$). For moderate-vigorous activity, increased risk was suggested ($p=.07$) for girls who spent 2 or more hours/day compared to less than 30 minutes/day (multivariable-adjusted categorical model, Table 2). However, we saw no evidence that total METS (from walking and moderate-vigorous activity) or recreational inactivity were associated with BBD (Table 2). Because vigorous activity is thought to modify breast cancer risk by affecting menstrual cycle characteristics, we further investigated vigorous (METS>6.0) physical activity at age 14yr among only those girls who were post-menarcheal

(by excluding 16% of girls still pre-menarcheal at 14yr). We found no evidence that vigorous activity might reduce BBD risk (continuous $OR=0.99/(hr/day)$, $p=.95$; categorical $OR=1.11$ for 1.5hr/day vs 15min/day, $p=.74$).

Though our estimates for the effects of moderate-vigorous activity and walking (in multivariable-adjusted models) were mutually adjusted, we consider here whether there is interaction in their effects. Our sample is too small to fit models with cross-classified (3×3) categories of moderate-vigorous activity by walking, but we were able to estimate the effect of continuous walking (hrs/day) within category of moderate-vigorous activity. Though no estimates were statistically significant, walking appeared most beneficial among girls with the least moderate-vigorous activity ($OR=.23/(hr/day \text{ of walking})$, $p=.38$); among girls in middle category of moderate-vigorous activity $OR=0.67/(hr/day \text{ walking})$ ($p=.34$), while among the most active girls, $OR=0.88/(hr/day \text{ walking})$ ($p=.71$). Additionally, we fit a model assessing the (2×2) interaction between moderate-vigorous activity and inactivity; no new insight was provided and the interaction was not significant ($p=.22$).

Baer and colleagues [12] earlier reported a U-shape association for high school physical activity (recalled in adulthood), in which middle levels of activity were protective but higher levels were not. We observed one minor U-shape pattern, for total METS at age 14yr: $OR=1.00$ (bottom tertile), $OR=0.72$ ($p=.17$) for middle tertile, and $OR=1.19$ ($p=.42$) for most active tertile.

Because we observed no statistically significant associations between BBD and moderate-vigorous activity, we further investigated a series of alternative physical activity questions (each from a single survey year) that correspond to moderate-vigorous activity, but were likely simpler for the participants to report (than time spent, during the past year, in each of 17 activities and sports). These alternative questions included "In general, how active are you?", and "During 7th to 9th grade" the number of seasons each year you played a sport that practiced regularly "like swimming, gymnastics, field hockey, basketball". Other questions were "In school, how many times per week do you participate in team sports?", and the total number of hours/wk of physical activity "like biking, swimming, working outdoors, or team sports" during each season of the past year but not a separate question for each sport or activity. For each of these alternative questions, when answered by 14yo girls, the estimated associations with BBD were null (not shown). However, for "In general, how active are you?" those who responded "average" had lower estimated BBD risks than those who reported being less active or more active than average, again suggesting a U-shape association, though these differences were not statistically significant.

We also attempted to investigate sleep (hours each night before school) among 14yr old girls. Because our sleep question appeared on only 2 surveys (1999 and 2001), data at age 14yr were available on a small subset of our cohort. Though no estimates were significant, the data did suggest that 7–8 hrs/night provided the lowest risk ($OR=0.78$ for 7–8hrs/night vs more or less, $p=.31$).

As this work is our first to investigate adolescent physical activity and inactivity, our earlier published results did not adjust for these factors. Table 3 summarizes the associations

between BBD and our previously investigated risk factors, now adjusting for physical activity and inactivity; these estimates are also based upon the currently larger number of BBD cases. Though a well-established risk factor for breast cancer, age at menarche was not associated with BBD. Childhood BMI and peak height growth velocity (cm/yr; PHV), derived from a girl's series of annual height measurements [22], remain significantly associated with risk for BBD, as does adolescent alcohol consumption [10]. Vegetable protein, peanut butter and nuts continue to be inversely associated with BBD risk [11]. Therefore, with additional BBD cases and with further adjustment for physical activity and inactivity, our previously-published findings persist.

Discussion

To our knowledge, this is the first investigation of physical activity (moderate-vigorous, walking) reported prospectively by adolescent girls, rather than recalled later in adult life, and their risk for BBD as young women. And no previous studies have considered adolescent sedentary activities (watching television-videos, playing video-computer games), or sleep. We found evidence that more time walking at 14yrs was associated with lower BBD risk. No statistically significant associations were observed for moderate-vigorous activity, total METS, inactivity, or sleep. Here we also confirmed (now with more cases, and with adjustment for physical activity and inactivity) our previously published associations between BBD and adolescent alcohol consumption [10], childhood adiposity and peak height growth velocity [22], and vegetable protein and peanut butter [11].

The earliest investigation of this topic involved a cross-sectional survey that found less BBD among former college athletes than among non-athletes [27], but college corresponds to a much older age period than we studied. However, our findings are partially consistent with a more recent analysis of high school physical activity and proliferative BBD, in that no benefit was observed for the highest levels of physical activity, but some protection was seen from middle range activities (strenuous activity 4–9mo/yr in high school, but not for >9mo) [12]. Combining exposures from grade 7 to age 22yr of strenuous and moderate activity, those authors found protection from 5–6.9hrs/week of activity, but not from more hrs/wk [12]. A separate investigation of lifetime physical activity found that lifetime walking reduced proliferative BBD risk (by 9% per hr/wk), but estimates were not presented separately for adolescence [28]. A recent review article concluded that there is little evidence linking adolescent physical activity with BBD [29].

The evidence for a link between adolescent physical activity and breast cancer is stronger. Lifetime strenuous activity (4 or more hrs/wk) reduced risk for columnar cell lesions, an early lesion in breast tumor progression [28], but adolescent activity was not presented separately. In other work, an impressive protective effect was found among women with greater hours/week of regular physical exercise, from menarche through young adulthood, for breast cancer diagnosed before age 41 [8]. The risk for pre-menopausal breast cancer had a significant inverse association with total physical activity during ages 12–22yr, and weaker associations for activity at older ages [7]. Brisk walking (5hrs/wk) by adult women was sufficient to reduce risk for post-menopausal breast cancer, which the evidence suggested may at least partially be acting on a non-hormonal pathway [30].

The mechanism whereby physical activity may reduce risk of breast cancer is likely hormonal, since moderate and vigorous physical activity delays the onset of menses and alters menstrual cycle characteristics, and reduces the female body's exposure to estrogen and other hormones [26,31]. On the other hand, physical activity appears to have no association with mammographic breast density, making it unlikely that its protective effect is mediated through breast density [32]. The fact that we found no association between adolescent moderate-vigorous activity and BBD is consistent with the fact that we similarly found no association between age at menarche and BBD (Table 3). An analysis of NHS women found that later age at menarche does not protect women with BBD against breast cancer, though women without BBD are protected by later menarche [33]. Furthermore, younger women with BBD were more likely to have non-proliferative BBD, and those who had a later age at menarche were instead at higher risk of breast cancer [34]. Still, it is puzzling that adolescent moderate-vigorous physical activity would have no association with BBD, while walking has a protective effect. Mechanisms to explain these inconsistencies are unclear, but may indicate different pathways to disease, including a different pathway from physical activity to the prevention of breast cancer.

The longitudinal design of this investigation comprises its major strength, as all exposure variables were collected, in real time, years prior to the reporting of BBD in this large cohort of girls from all over the US. Though all our models controlled for age and childhood adiposity, and other potential confounders were in multivariable-adjusted models, some residual and unmeasured confounding may remain. We cannot exclude the possibility of incomplete adjustment, or confounding through variables not considered, but little is known about childhood risk factors for BBD. Although our cohort is not representative of US females, the comparison of risks within our cohort should still be valid and generalizable [35]. Because our participants are daughters of nurses, this reduces confounding by socioeconomic and other unmeasured factors, while enhancing the accuracy of the data.

The most serious limitation is our small number of cases, although we did obtain significant odds ratios for adolescent walking (Table 2) and for a number of other factors (Table 3). Another limitation was the necessity to collect data by self-report, but alternatives were not feasible. Time spent walking may be better reported than moderate and vigorous activities, which occur sporadically in some girls. When we looked at alternative survey questions related to moderate-vigorous activity but simpler to report, such as times per week in practice and play for a team, estimated associations remained null. On the whole, these girls appear to be very active, possibly because their mothers are nurses, and this might explain the lack of an association for physical activity. Reporting errors for activity and inactivity were likely non-differential with respect to subsequent BBD, possibly biasing our estimates toward the null. The racial/ethnic makeup of our cohort (95% white/non-Hispanic) hinders race/ethnic group-specific analyses and generalization to these other races/ethnicities.

In conclusion, we assessed the relationship between biopsy-confirmed BBD in young women and their physical activities and sedentary behaviors recorded during adolescence, a period previously demonstrated to be critical for the development of breast cancer [2–5] and other adult diseases. We found evidence that adolescent girls who walked the most were at lower risk for BBD, but no associations were seen with moderate-vigorous activity or

recreational inactivity. Because our number of cases was relatively small, and because some exposures may have longer latency periods, continued follow-up of this cohort will be critical to re-assess these results as new cases of BBD are diagnosed.

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Table 1

Physical activities and recreational inactivity (TV, videos, video/computergames) at age 14yr and other characteristics of 7034 females in the Growing Up Today Study, according to total METS per day at age 14yr. (Total METS includes walking and moderate to vigorous physical activity.) Shown are Mean (SD) or %.

Range	Tertile of METS/day at age 14yr		
	T1 (0–7.40)	T2 (7.41–13.95)	T3 (13.96–42.73)
N =	2344	2345	2345
Activities and Inactivity at age 14yr			
METS/day	4.28 (1.99)	10.43 (1.87)	20.91 (5.96)
Moderate/Vigorous Activity (hrs/day)	0.69 (.52)	1.50 (.58)	2.80 (.98)
Walking (hrs/day)	0.18 (.23)	0.28 (.33)	0.52 (.46)
Recreational Inactivity (hrs/day)	2.61 (1.68)	2.55 (1.54)	2.58 (1.62)
Sleep (hrs/night)	7.64 (1.03)	7.55 (1.03)	7.42 (1.15)
Other Characteristics			
Biopsy-confirmed BBD ^a	1.8%	1.5%	2.3%
Age (yrs) at Baseline (1996)	11.93 (1.60)	11.91 (1.60)	12.21 (1.61)
Childhood BMI (kg/m ²) ^b	18.31 (3.59)	18.10 (3.26)	18.02 (3.11)
Age at menarche (yr)	12.86 (1.19)	12.87 (1.21)	12.87 (1.22)
Pregnancy ever ^c	5.2%	4.3%	4.0%
Teen alcohol (drinks/day)	0.15 (.34)	0.21 (.42)	0.27 (.46)
Age 14 peanut butter, nuts (servings/wk)	1.04 (1.43)	1.18 (1.51)	1.23 (1.53)
Age 14 vegetable protein (gm/day) ^d	24.6 (4.7)	24.9 (5.4)	24.8 (6.0)
Peak Height Growth Velocity (cm/yr)	8.25 (2.71)	8.35 (2.67)	8.19 (2.76)
Family History of Breast Disease:			
In Mother or Maternal Aunt: Breast Cancer	7.0%	7.6%	6.8%
In Mother: BBD	16.1%	19.8%	19.8%

^aBenign breast disease in participant, reported to November 1, 2013.

^bBMI at age 10yr, derived from baseline BMI and adjusted to age 10yr [20] using CDC BMI growth charts.

^cPregnancy reported through 2005 survey.

^dEnergy-adjusted.

Table 2

Risk for biopsy-confirmed BBD in young women (133 cases and 6901 non-cases) related to physical activities and inactivity at age 14yr. All models adjust for baseline age and baseline BMI.

	Never Reported Biopsy-Confirmed		Continuous Risk Factors		Highest vs Lowest Category ^a	
	BBD	BBD cases	Age-BMI-adj	Multivar-adjusted	Age-BMI-adj	Multivar-adj
	Mean (SD)	Mean (SD)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
<u>Physical Activities and Inactivity at age 14yr</u>						
Mod & vigorous (hrs/day)	1.66 (1.13)	1.81 (1.18)	1.09 (.94–1.27)	1.09 ^b (.93–1.28)	1.65 (.87–3.12)	1.84 ^b (.96–3.55) *
Walking (hrs/day)	0.33 (.38)	0.30 (.40)	0.80 (.49–1.30)	0.80 ^b (.47–1.34)	0.66 (.41–1.06) *	0.61 ^b (.37–.99) **
Total Mets/day	11.86 (7.84)	12.65 (7.78)	1.01 (.99–1.03)	1.01 ^c (.99–1.03)	1.20 (.80–1.81)	1.19 ^c (.78–1.82)
Inactivity (hrs/day)	2.58 (1.62)	2.49 (1.40)	0.98 (.88–1.10)	0.96 ^b (.85–1.09)	1.02 (.67–1.55)	1.02 ^b (.67–1.56)
(TV, videos, computer/videogames)						

^aFor moderate/vigorous physical activity, top vs bottom is 2hrs/day vs 30min/day. For walking, top vs bottom is 30min/day vs 15 min/day. For METS, comparison is top vs bottom tertile. For inactivity, top vs bottom is 3hrs/day vs <2 hrs/day.

^bFrom multivariable models including age 14yr moderate/vigorous activity, walking, inactivity, intakes of peanut butter/nuts, total energy intake, adolescent alcohol consumption, pregnancy history, age at menarche, and family history of breast disease.

^cFrom multivariable models including age 14yr total METS, inactivity, intakes of peanut butter/nuts, total energy intake, adolescent alcohol consumption, pregnancy history, age at menarche, and family history of breast disease.

* P<0.10

** P<0.05

Table 3

Risk factors previously investigated and published (on same cohort), but the estimated risks shown below are based upon the currently available larger numbers of BBD cases (133 cases, 6901 non-cases), and the multivariable-adjusted models further include physical activity and inactivity variables. All models include baseline age and BMI.

	Never Reported Biopsy-Confirmed		Continuous Risk Factors		Highest vs Lowest Category ^a	
	BBD	BBD cases	Age-BMI-adj	Multivar-adjusted	Age-BMI-adj	Multivar-adj
	Mean (SD)	Mean (SD)	OR (p-value)	OR (p-value)	OR (p-value)	OR (p-value)
Childhood BMI (kg/m ²) ^b	18.2 (3.3)	17.3 (2.6)	0.91 (.01)	0.91 ^c (.01)	0.51 (.01)	0.49 ^c (.01)
Menarche age (yr)	12.9 (1.2)	13.0 (1.1)	1.03 (.74)	1.02 ^c (.81)	1.04 (.85)	1.10 ^c (.68)
Peak Height Growth Velocity (PHV; cm/yr)	8.26 (2.7)	8.59 (2.6)	1.09 (.06)	1.09 ^d (.06)	1.81 (.04)	1.88 ^d (.03)
Teen alcohol (drinks/wk)	1.47 (2.9)	2.14 (3.6)	1.04 (.08)	1.05 ^e (.067)	1.57 (.04)	1.55 ^e (.048)
Age 14yr Diet (energy-adjusted):						
Veg Protein (10 gm/day)	2.48 (0.54)	2.38 (.46)	0.70 (.048)	0.67 ^f (.03)	0.66 (.049)	0.68 ^f (.067)
Peanut Butter, Nuts (servings/wk)	1.15 (1.49)	0.85 (1.24)	0.84 (.02)	0.82 ^e (.015)	0.57 (.03)	0.57 ^e (.03)

^aCategorical comparisons are top vs bottom tertiles, except for alcohol, where top vs bottom comparison is 3+ drinks/wk vs 0–<1 drink/wk.

^bBMI at age 10yr, derived from baseline BMI and adjusted to age 10yr [20] using CDC BMI growth charts.

^cFrom multivariable-adjusted model including childhood BMI, age at menarche, and baseline age, peanut butter/nuts, total energy intake, moderate/vigorous activity, walking, and inactivity.

^dFrom multivariable-adjusted model including PHV (peak height velocity), childhood BMI, age at menarche, baseline age, peanut butter/nuts, total energy intake, moderate/vigorous activity, walking, and inactivity. PHV data available only for girls who were still growing at baseline (3999 non-cases and 74 BBD cases).

^eFrom multivariable-adjusted model including adolescent alcohol intake, intakes of peanut butter, nuts, total energy at age 14yr, pregnancy ever, baseline age, childhood BMI, and age 14 moderate/vigorous activity, walking, and inactivity.

^fFrom multivariable-adjusted model including vegetable protein (energy-adjusted) at age 14yr, adolescent alcohol intake, pregnancy ever, baseline age, childhood BMI, and age 14 moderate/vigorous activity, walking, and inactivity.