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Lifetime Physical Activity and the Incidence of Proliferative Benign Breast Disease

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Abstract

Background—Exercise is a modifiable factor that is inversely related to risk for breast cancer. To determine if physical activity has a preventative effect on development of premalignant breast lesions, we examined the association between exercise and the incidence of proliferative benign breast disease.

Methods—In 1997, the Nurses' Health Study II cohort reported levels of physical activity during adolescence and adulthood using a validated recall instrument. We followed 40,318 participants free from BBD or cancer prospectively for four years and confirmed 232 proliferative benign breast lesions by centralized pathology review. Cox proportional hazards models estimated the age-adjusted and multivariable-adjusted relative risks for physical activity and proliferative benign breast disease (BBD).

Results—We observed a significant inverse association for walking and incidence of BBD, risk was reduced by 9% per hour of walking (95% CI 0% to 17%), (p trend=0.05). Despite a small number of cases, risk of columnar cell lesions also suggested an inverse association with strenuous activity (RR for 4 or more hours of strenuous activity per week = 0.62; 0.31–1.22 compared to <1 hour per week).

Conclusions—This study suggests that exercise may be inversely associated with the risk of developing proliferative benign breast disease, one of the earliest steps in the development of breast cancer.

Introduction

Physical activity is a modifiable factor that is associated with a decreased risk for both premenopausal and postmenopausal breast cancer (1, 2). The mechanism for this protective effect remains unclear. Exercise may decrease the amount of mitogenic hormones available in the body, such as estrogen, insulin-like growth factor (IGF), and insulin (3, 4). By decreasing the bioavailability of sex hormones such as estrogen, physical activity can

significantly delay onset of menarche and alter the length and regularity of subsequent menstrual cycles, all of which can influence one's risk for developing breast cancer (5, 6).

Studies have shown that exercise during both adolescence and adulthood contributes to a decreased risk for developing invasive breast cancer. This malignancy, like other diseases, has several stages of development. When during the course of breast cancer development physical activity actually operates to reduce risk is at this time an unanswered question.

Proliferative benign breast disease (BBD) has long been considered one of the first steps in the progression to breast cancer (7). A history of non-atypical proliferative BBD increases risk of breast cancer by 1.5 to 2-fold and the presence of atypia increases risk 3.5 to 5-fold (8). More recent studies suggest that columnar cell lesions (including columnar cell change, columnar cell hyperplasia, and flat epithelial atypia) may be the first histopathologic change that occur on the pathway to breast cancer (9).

To determine if physical activity has an early preventative effect on breast cancer development, in this study we examined the effect of childhood, adolescent, and adult physical activity exposure on the incidence of proliferative BBD in the Nurses' Health Study II cohort. A previous analysis of this study population, using a more limited assessment of adolescent physical activity, reported inconsistent associations with incidence of proliferative BBD (10). A nested case-control study performed in Australia looked at cases of proliferative epithelial breast disease and reported average weekly amounts of physical activity, showing no definitive association, but the authors suggested further examination to explore this issue (11). In contrast to previous studies, in our analysis, we utilized a more detailed assessment of physical activity that includes activity during all ages, details specific exercise activities, and takes into consideration the metabolic effort required to complete each exercise task (1, 12). We also extended our analysis to include an assessment of the association of physical activity with columnar cell lesions, which have been suggested to be among the earliest lesions in breast tumor progression. Our work and others suggest that approximately 3–28% of benign breast biopsies contain columnar cell lesions (13–15). To our knowledge, this is the first prospective study that provides this kind of detailed and comprehensive assessment of exercise in relation to the development of proliferative BBD and columnar cell lesions.

Participants and Methods

Study Population

The Nurses' Health Study II (NHSII), a cohort study, was established in 1989. At baseline, the study population included 116,606 female registered nurses who were 25 to 42 years of age at the time. Participants were asked to fill out a baseline questionnaire on cancer risk factors. Every two years since the onset of the study, the women are asked to fill out a follow-up questionnaire about their health and lifestyle (16); these can be found online (17). In 1997 and 2001, questions addressing levels of physical activity during adolescence and adulthood were included. The response rate for these questionnaires has been around 90% (1). Deaths were confirmed by the National Death Index (18, 19).

In this prospective analysis, we followed the participants for a total of four years, beginning in 1997, the year in which they reported levels of adolescent and adult physical activity. At the beginning of this analysis, the women were 32 to 51 years of age. 80,252 women filled out the long form questionnaire in 1997 that included recall of adolescent physical activity. Women were excluded from this study if they belonged to any one of the following categories: missing physical activity data ($n=3,100$), self-reported BBD before 1997 ($n=34,147$), death before 1997 ($n=1,927$), self-reported cancer (except non-melanoma skin

cancer) before 1997 (n=1,380), and breast biopsy before 1997 (n=1,307). 40,318 women were eligible for the study after these exclusions. Women were censored during each follow-up period if they had a report of cancer, or died during the previous time period. In addition, a small number of women were also censored if they reported a BBD and we were unable to obtain pathology specimens from their biopsy.

The Human Subject Committee at Brigham and Women's Hospital in Boston, Massachusetts approved this study. Written informed consent was assumed upon completion and return of the questionnaire.

Physical Activity Assessment

Physical activity was measured as described in Maruti et al (1). In summary, women reported average number of hours per week they spent walking and engaged in moderate or strenuous activity outside of work (leisure-time physical activity). They were specifically asked to report levels of physical activity during five age periods: grades 7–8 (ages 12–13), grades 9–12 (ages 14–17), ages 18–22, ages 23–29, and ages 30–34. For each period, participants reported the average hours per week they engaged in each of three activity categories, strenuous (e.g., running, aerobics, swimming laps), moderate (e.g., hiking, walking for exercise, casual cycling), and walking to a from school or work. Participants were also asked in 1997 and in 2001 to report average number of hours spent jogging, running, bicycling, playing racquet sports, swimming laps, walking or hiking, and doing calisthenics or aerobics during the previous year. In this study, only leisure-time physical activity was considered because occupational activity levels were similar among participants. Furthermore, evaluation of physical activity measures showed good reproducibility (average correlation $r=0.76$ for strenuous, $r=0.70$ for strenuous plus moderate, and $r=0.64$ for total activity) and validity ($r=0.79$, 95% CI = 0.64 to 0.88) (1, 10, 20). Since different activities require different levels of physical exertion, each activity was assigned a metabolic equivalent (MET) value. This MET value equals the metabolic rate of the activity divided by the resting metabolic rate. Total physical activity was calculated as MET-hours per week, the average number of hours per week spent engaged in an activity multiplied by its MET value as previously reported (1).

Assessment of Incident Proliferative Benign Breast Disease

In each biennial questionnaire, the women were asked if they had received a diagnosis of BBD by a physician since the last questionnaire. They were also asked whether or not that diagnosis was confirmed by aspiration and/or biopsy. Women with a self-reported diagnosis of BBD were subsequently contacted to confirm the diagnosis and seek permission to review their biopsy samples. Collection of these specimens has been described previously (21). Briefly, over 80% of eligible participants confirmed their BBD diagnosis and granted permission for review of their biopsy records and pathology slides. Pathology materials were obtained and reviewed for 87% of those who had given permission. Between 1997 and 2001, 427 women confirmed their diagnosis of BBD and had valid pathology specimens for review by study pathologists. Of these 404, also completed the physical activity questionnaires required for lifetime assessment of physical activity. An additional 71 women excluded over follow-up due to exclusion criteria including cancer diagnosis prior to BBD, or date of BBD diagnosis was prior to the return of the questionnaire.

Biopsy samples collected from the pathology departments of the various hospitals were coded and provided to study pathologists (LCC, SJS, JLC) for independent blinded review. This centralized pathology review classified BBD lesions according to the Dupont and Page criteria (22) as nonproliferative, proliferative without atypia, and proliferative with atypia (atypical ductal hyperplasia and atypical lobular hyperplasia). Lesions with intraductal

papilloma, radial scar, sclerosing adenosis, fibroadenoma, fibroadenomatous change, or moderate to florid ductal hyperplasia in the absence of atypical hyperplasia were diagnosed as proliferative without atypia. Biopsy samples with atypia or questionable atypia were analyzed by two pathologists who determined a consensus decision. Proliferative lesions of the ducts and lobules are known to be associated with an increased risk for breast cancer. In particular, atypical hyperplasia is considered to be a marker for later development of breast cancer, with a relative risk of 3.0 (95% CI = 2.1–4.1) (23, 24). Therefore, proliferative BBD with or without atypia was chosen as the main outcome of interest in this analysis, an approach that is consistent with previous analyses in this cohort.

Assessment of Incident Columnar Cell Lesions

Study pathologists determined the presence of columnar cell lesions (CCL) in the benign breast biopsy samples. Women who were diagnosed with BBD between 1999 and 2001 were further assessed for the presence of CCL subtypes (columnar cell change, columnar hyperplasia, and flat epithelial atypia) (25). Additional follow-up years were not assessed for the presence of CCL. These cases were divided into presence or absence of CCL for analysis purposes.

Covariates

Height and childhood body shape were obtained on the 1989 questionnaire. Alcohol intake was reported in 1995. Parity, age at first birth, oral contraceptive use, and body weight were obtained on both the 1997 and 1999 questionnaires. Family history of breast cancer (mother and/or sister) was reported in 1989 and 1997.

Statistical Analysis

Participants contributed a total of 161,807 person-years of follow-up between 1997–2001. Person-time was calculated for each participant from the date of questionnaire return in 1997 until a diagnosis of benign breast disease, death, or the end of follow-up on June 1, 2001, whichever came first. Person-time was assigned to the appropriate level of physical activity and covariate categories at the beginning of each 2-year questionnaire cycle.

Cox proportional hazards were used to determine the age-adjusted and multivariable-adjusted relative risks for proliferative benign breast disease and their appropriate 95% confidence intervals. The time scale for the hazard model was age calculated in months. Physical activity was assessed as walking, moderate, strenuous (hours per week), and total physical activity (MET-hours per week) divided into quintiles. Relative risks were calculated as the incidence of proliferative benign breast disease in each group compared to the incidence of the disease in women falling in the lowest groups of physical activity.

Since proliferative BBD is known to be associated with an increased risk for breast cancer, we adjusted for known breast cancer risk factors in the multivariable analyses: age (months), average childhood body shape (categorical pictogram scale from 1 to 5), use of oral contraceptives (never, past use, current use), family history of breast cancer in mother and/or sister (yes, no), parity and age at first birth (nulliparous; parity 1–2, age at first birth < 25; parity 1–2, age at first birth 25–29; parity 1–2, age at first birth ≥ 30; parity ≥ 3, age at first birth < 25; parity ≥ 3, age at first birth 25–29; parity ≥ 3, age at first birth ≥ 30), current alcohol consumption (none, >0.0–1.4 g/d, 1.5–2.9 g/d, 5.0–9.9 g/d, ≥ 10 g/d), and height (inches, continuous). BMI was considered an intermediate variable in the causal pathway between physical activity and breast cancer. Therefore, this was not included as a core covariate but assessed in additional models (See “Results”). Physical activity was modeled as a continuous variable in order to test for linear trend. A two-sided *p*-value of <0.05 was

considered statistically significant. Analysis was performed with SAS version 9.0 (SAS Institute Inc, Cary, NC).

Results

Between 1997 and 2001, 333 women in this cohort of 40,318 women had a confirmed diagnosis of BBD upon review of their biopsy samples by the study pathologists and were eligible for the current study. Of these women 101 had normal breast tissue or non-proliferative lesions, whereas 232 had a diagnosis of proliferative BBD with or without atypia between 1997 and 2001. 97 cases of columnar cell lesions were also confirmed among these women.

Table 1 illustrates key characteristics of the 40,318 women in our study when they filled out the physical activity questionnaire in 1997. The participants were stratified according to their average lifetime total activity. Studies have shown that a variety of factors such as parity, age at first birth, age at menarche, use of oral contraceptives, and childhood BMI are associated with one's risk for developing proliferative BBD (10, 26). We also considered different risk factors known to be associated with breast cancer. Age-adjusted prevalence data showed that women who were more physically active were more likely to be younger, nulliparous, taller, less overweight during childhood, have lower BMIs at age 18, and have lower current BMIs. Women who were more physically active were also more likely to consume greater than 10 grams of alcohol per day and be current smokers.

We next assessed the relationship between total lifetime physical activity, different intensities of physical activity, and risk for developing proliferative BBD (Table 2). For this analysis we divided average lifetime leisure-time activity into four different categories: strenuous, moderate, walking, and total physical activity. Each category was further divided into quintiles of intensity. We observed a significant inverse association for walking and incidence of proliferative breast disease (p -trend=0.05). Walking was associated with 9% reduction in risk of proliferative BBD per hour of walking per week ($RR=0.91$, 95% $CI = 0.83$ to 1.0 , per hour of walking per week). Additional adjustment for other types of physical activity did not materially change the results. In addition, we also explored a non-linear relationship between lifetime physical activity and proliferative activity using cubic splines. However, the data support a linear relationship.

As columnar cell lesions have been postulated to be among the earliest morphologic changes in the pathway to breast cancer (27), we next evaluated physical activity in relation to risk of these lesions (Table 3). Although we had limited power due to the small number of cases, we observed a similar inverse relation between activity and risk of columnar cell lesions. Total physical activity appeared to have an inverse association with the development of columnar cell lesions and women engaged in 39–53.9 MET-h/wk of total physical activity had a multivariable-adjusted relative risk of 0.63 (95% $CI = 0.33$ to 1.19 , p -trend = 0.22) compared to women with less than 21 MET-h/wk.

Results for strenuous and moderate activity were not significant. We observed no significant difference in the association of physical activity with proliferative BBD during different age periods though power was limited due to the small number of cases (data not shown).

Finally, we performed a stratified analysis dividing the women into groups of those with BMIs at age 18 of less than 21 kg/m^2 and greater than 21 kg/m^2 (Table 4). One case subject was missing data on BMI at age 18. In this sub-analysis, women with implausible values for BMI (<15 or >55) were excluded. Women who had lower BMIs at age 18 appeared to have a stronger inverse trend demonstrating that increasing levels of physical activity were associated with lower incidences of disease. However, a formal test for interaction was not

statistically significant ($p = 0.49$). A stratified analysis dividing the women into groups of those with BMIs in 1997 of less than 25 kg/m² and greater than 25 kg/m² showed no significant difference between the two groups. Because benign breast diseases are detected primarily as a function of mammographic screening, we also conducted secondary analyses restricted to women who reported having had a mammogram in the previous two years. The results from these analyses were very similar to those presented from the entire population. For example, among women who were screened, walking was associated with a marginally significant 7% reduction in risk of proliferative BBD per hour of walking per week (RR=0.93, 95% CI = 0.84 to 1.02, per hour of walking per week) (Supplementary Table 1).

Discussion

In this prospective study, increasing levels of lifetime total physical activity were inversely associated with the incidence of proliferative BBD and columnar cell lesions, both of which are considered early stages in the development of breast cancer. Specifically, women engaged in 39–53.9 MET-h/wk of physical activity seem to gain the most health benefit from their exercise and had a magnitude of risk reduction comparable to that observed in this cohort for invasive breast cancer. 39 MET-h/wk is equivalent to approximately 13 h/wk of walking or 3.25 h/wk of running. When stratified by BMI at age 18, women with lower BMIs at age 18 where physical activity may have impacted energy balance to avoid weight gain, showed a stronger inverse trend of a decrease in incidence of proliferative BBD with increasing levels of physical activity, although this analysis was limited in power.

Our study is the first to examine prospectively the association between a detailed assessment of lifetime physical activity and proliferative BBD. Not only are there few studies that have assessed this relationship, but these previous analyses utilized limited measures of physical activity assessment. Specifically, in a previous study looking at physical activity and proliferative BBD in the Nurses' Health Study II cohort (10), the researchers used a less detailed measures of physical activity, exclusively focused on physical activity during adolescence, and not during all age groups, and did not consider the varying metabolic requirements of different exercise tasks. A second study using a case-control design only considered the participants' reported average level of weekly physical activity as an assessment for exercise (11).

The manner in which we assessed and modeled physical activity was identical to a previous study of breast cancer conducted with the Nurses' Health Study II cohort, and has been shown to be reproducible (1, 10). In that prospective analysis, we reported the association between physical activity and incidence of premenopausal breast cancer (1). Specifically, the study demonstrated that women engaged in at least 39 MET-h/wk of total physical activity lowered their risk for developing premenopausal breast cancer by 23% (RR = 0.74, 95% CI = 0.56 to 0.97). The magnitude of this inverse association was very similar to the results we obtained from our study of premalignant endpoints using proliferative BBD and columnar cell lesions. These results imply that physical activity may act to be protective against breast cancer in the earliest stages of development, i.e. proliferative BBD and columnar cell lesions. Furthermore, it is possible that women with lower BMIs at age 18 may see the benefits of physical activity more strongly. This may reflect the physiologic impact of energy balance on delay in menarche and altered menstrual cycles which decreases exposure to hormones such as estrogen (28).

The exact mechanism by which physical activity helps prevent breast cancer remains unknown. Estrogen, insulin-like growth factor, and insulin have all been implicated as having causal effects on the development of breast cancer (3, 4). As mentioned earlier, exercise lowers levels of these hormones. By delaying menarche and altering the regularity

and length of menstrual cycles, physical activity decreases the body's exposure to estrogen (28). Furthermore, while insulin increases bioavailability of IGF and estrogen, exercise decreases levels of insulin (29–31). The results of this study suggest that the hormone-lowering effects of physical activity are not only protective against breast cancer, but also beneficial at younger ages when women first develop BBD. Furthermore, researchers can now utilize proliferative breast disease and columnar cell lesions as new, additional endpoints in their studies to better understand the biological basis of the benefits of physical activity.

There are both strengths and limitations to this study. First, the detailed assessment of physical activity in our study allowed for a more thorough analysis of exercise and proliferative BBD. Using a prospective analysis eliminates recall bias and will result in non-differential misclassification of recalled physical activity. Furthermore, a centralized review of pathology slides allowed for uniform classification of BBD and columnar cell lesions. However, there are limitations. First, physical activity was assessed using a self-administered questionnaire and also required the participant to recall past levels of activity. Despite these limitations, the physical activity measures showed good reproducibility and validity (1, 10, 20). Second, we were unable to obtain pathology specimens on all participants reporting a BBD biopsy. However, women we were able to obtain specimens on were very similar with respect to lifestyle characteristics and adolescent physical activity levels compared with the women we were unable to obtain specimens from. Thus, although this reduced our total number of cases contributing to the analysis and reduced our power to detect associations; it is unlikely to have resulted in a selection bias. Third, our study followed the women for four years limiting the number of cases confirmed by central pathology review, and reducing the power of this analysis. Thus, chance remains a possible explanation for our findings. Nevertheless the magnitude of associations is consistent across the endpoints of benign lesions and invasive breast cancer. Additional follow-up will be required to refine these associations. Finally, benign breast lesions are detected primarily through mammographic screening, which could result in detection bias. However, because this population of women is health professionals, they are more health conscious than the general population. Among women greater than 40, for whom screening was recommended at this time, 85% of the women reported having a mammogram in the previous two years. In secondary analyses restricted to women reporting a mammogram, there were no noticeable differences in results indicating the current results are unlikely to be influenced by detection bias. The frequency of CCL is unknown in an unscreened population. The current analysis assumes that women without a biopsy do not have CCL. Although there is evidence that CCL is lower among women with nonproliferative BBD, compared with proliferative BBD, there is likely to be misclassification of the CCL outcome. However, this misclassification is likely nondifferential with respect to physical activity during high school, which would result in attenuation of the observed association.

In conclusion, our study results imply that in the prevention of breast cancer, physical activity may help reduce the risk of developing proliferative BBD and columnar cell lesions, two of the earliest steps in the development of breast cancer. These results suggest that the benefits of physical activity may begin to operate at a relatively early time point in the development of breast cancer and supports results from invasive premenopausal breast cancer which emphasize the importance of consistent physical activity throughout one's lifetime for maximum breast health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Characteristics of 40 318 women 32 to 51 years of age in 1997 according to categories of average lifetime total activity, Nurses' Health Study II

Table 1

Characteristic	MET-h/wk (median)						p
	<21 (14.5)	21-29.9 (25.5)	30-38.9 (34.3)	39-53.9 (45.4)	>= 54 (68.2)		
No. of participants	10050	7759	6940	7647	7922		
Age, y	43.0	42.3	41.7	41.3	41.1		<.0001
Mother or sister with breast cancer, %	7.9	7.8	7.8	7.9	7.5		0.73
Current oral contraceptive user, %	8.9	9.5	9.6	9.7	9.8		0.38
Nulliparous, %	17.4	17.7	18.0	19.5	22.3		<.0001
Parity	2.3	2.34	2.3	2.3	2.3		0.002
Age at first birth	26.4	26.67	26.7	26.8	26.7		<.0001
Height, inches	64.8	64.9	64.9	65.0	65.1		<.0001
Birthweight, GE 8.5 lbs, %	11.6	12.3	11.6	12.1	12.1		0.06
Overweight during ages 5 and 10, %	7.1	6.6	6.4	5.7	5.6		<.0001
BMI at age 18, kg/m ²	21.7	21.4	21.3	21.2	21.1		<.0001
Current BMI, kg/m ²	27.2	26.3	25.9	25.9	25.5		<.0001
Alcohol intake GE 10 g/d, %	6.6	9.1	8.8	10.3	11.0		<.0001
Current smoker, %	8.9	9.2	9.4	9.3	11.0		<.0001
Age at menarche, <12 y, %	26.1	23.1	23.7	22.6	23.8		0.65
Television watching, h/wk	8.7	8.3	8.3	8.4	8.6		0.20

Table 2

Relative risk of proliferative benign breast disease by intensity of lifetime average physical activity, Nurses' Health Study II, 1997–2001

Type of activity	Person-years	No. of Prol. BBD	Age-adjusted RR	Multivariable-adjusted RR (95% CI)	Multivariable-adjusted RR (95% CI)*
Strenuous, h/wk					
<1.0	34803	55	1.00 (referent)	1.00 (referent)	1.00 (referent)
1.0–1.9	40018	64	1.01	1.02 (0.71 to 1.47)	1.01 (0.70 to 1.46)
2.0–2.9	32244	41	0.84	0.85 (0.56 to 1.28)	0.83 (0.55 to 1.27)
3.0–3.9	21928	35	1.07	1.08 (0.70 to 1.66)	1.06 (0.67 to 1.67)
4.0	32814	37	0.75	0.77 (0.50 to 1.18)	0.75 (0.46 to 1.21)
<i>P</i> trend				0.13	0.12
Moderate, h/wk					
<1.0	18591	31	1.00 (referent)	1.00 (referent)	1.00 (referent)
1.0–1.9	41154	53	0.79	0.78 (0.50 to 1.22)	0.82 (0.52 to 1.29)
2.0–2.9	36281	59	0.99	0.99 (0.64 to 1.53)	1.08 (0.69 to 1.69)
3.0–3.9	25794	30	0.71	0.72 (0.43 to 1.19)	0.81 (0.48 to 1.37)
4.0	39987	59	0.91	0.91 (0.58 to 1.41)	1.09 (0.66 to 1.78)
<i>P</i> trend				0.89	0.50
Walking, h/wk					
<0.5	30352	42	1.00 (referent)	1.00 (referent)	1.00 (referent)
0.5–0.9	32234	59	1.28	1.24 (0.83 to 1.85)	1.25 (0.83 to 1.86)
1.0–1.4	28595	42	1.02	1.01 (0.65 to 1.55)	1.02 (0.66 to 1.56)
1.5–2.4	35704	44	0.85	0.85 (0.56 to 1.31)	0.87 (0.56 to 1.33)
2.5	34923	45	0.91	0.92 (0.60 to 1.41)	0.94 (0.60 to 1.46)
<i>P</i> trend				0.05	0.06
Total activity, MET-h/wk					
<21.0	40240	63	1.00 (referent)	1.00 (referent)	1.00 (referent)
21.0–29.9	31109	53	1.12	1.13 (0.78 to 1.63)	1.13 (0.78 to 1.63)
30.0–38.9	27793	40	0.94	0.95 (0.63 to 1.41)	0.95 (0.63 to 1.41)
39.0–53.9	30649	35	0.76	0.76 (0.50 to 1.16)	0.76 (0.50 to 1.16)
54.0	32016	41	0.85	0.87 (0.58 to 1.30)	0.87 (0.58 to 1.30)

Type of activity	Person- years	No. of Prol. BBD	Age-adjusted RR	Multivariable- adjusted RR (95% CI)	Multivariable- adjusted RR (95% CI) *
<i>Ptrend</i>					0.18

* additionally adjusted for other types of physical activity

Table 2

Relative risk of columnar cell lesions by intensity of lifetime physical activity, Nurses' Health Study II, 1997–2001

Type of activity	Person-years	No. of CCL	Age-adjusted RR	Multivariable-adjusted RR (95% CI)
Sitrenuous, h/wk				
<1.0	34803	26	1.00 (referent)	1.00 (referent)
1.0–1.9	40018	26	0.90	0.90 (0.52 to 1.56)
2.0–2.9	32244	17	0.75	0.75 (0.40 to 1.39)
3.0–3.9	21928	15	1.01	1.00 (0.53 to 1.92)
4.0	32814	13	0.60	0.62 (0.31 to 1.22)
<i>P</i> trend				0.08
Moderate, h/wk				
<1.0	18591	17	1.00 (referent)	1.00 (referent)
1.0–1.9	41154	23	0.62	0.60 (0.32 to 1.13)
2.0–2.9	36281	20	0.62	0.60 (0.31 to 1.15)
3.0–3.9	25794	14	0.60	0.59 (0.29 to 1.20)
4.0	39987	23	0.67	0.66 (0.35 to 1.25)
<i>P</i> trend				0.83
Walking, h/wk				
<0.5	30352	14	1.00 (referent)	1.00 (referent)
0.5–0.9	32234	24	1.48	1.47 (0.76 to 2.86)
1.0–1.4	28595	23	1.60	1.61 (0.82 to 3.14)
1.5–2.4	35704	16	0.88	0.88 (0.43 to 1.82)
2.5	34923	20	1.14	1.19 (0.60 to 2.38)
<i>P</i> trend				0.20
Total activity, MET-h/wk				
<21.0	40240	32	1.00 (referent)	1.00 (referent)
21.0–29.9	31109	21	0.90	0.89 (0.51 to 1.55)
30.0–38.9	27793	12	0.57	0.56 (0.28 to 1.09)
39.0–53.9	30649	14	0.62	0.62 (0.33 to 1.18)
54.0	32016	18	0.78	0.80 (0.45 to 1.45)
<i>P</i> trend				0.22

Table 4

Relative risks of proliferative benign breast disease by total lifetime activity, stratified by BMI at age 18, Nurses' Health Study II, 1997–2001*

Activity, MET-h/wk	BMI, 18 yrs < 21 kg/m ²		BMI, 18 yrs ≥ 21 kg/m ²	
	No. of prol. BBD	RR (95% CI)	No. of prol. BBD	RR (95% CI)
	139		92	
<21.0	39	1.00 (referent)	24	1.00 (referent)
21.0–29.9	30	0.95 (0.59 to 1.55)	23	1.365 (0.76 to 2.44)
30.0–38.9	23	0.80 (0.47 to 1.34)	17	1.20 (0.64 to 2.27)
39.0–53.9	24	0.76 (0.45 to 1.28)	11	0.70 (0.34 to 1.44)
54.0	23	0.69 (0.41 to 1.17)	17	1.09 (0.57 to 2.06)
<i>P</i> trend		0.16		0.46