Published in final edited form as:

Breast Cancer Res Treat. 2017 August ; 164(3): 697–705. doi:10.1007/s10549-017-4276-7.

Childhood and teenage physical activity and breast cancer risk

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Abstract

Purpose—Adult physical activity is associated with reduced breast cancer risk, but few studies have evaluated activity before adulthood. Early life may be an important period because of rapid breast development and hormonal changes. This study contributes new information by examining childhood (age 5–12) and teenage (age 13–19) activity separately and overall.

Methods—The Sister Study is a cohort of 50,884 women aged 35–74. Women reported age 5–19 sports/exercise activities and age 10 and 16 unstructured activities. Both hours and MET-hours of activity were considered in association with breast cancer overall, by ER status, and menopausal status. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with Cox proportional hazards models.

Results—2,416 cases were diagnosed during follow-up (mean=6.4 years). Participation in 7+ hours (vs <1 hour) per week of sports/exercise during ages 5–19 was associated with reduced breast cancer risk (HR=0.75; 95% CI: 0.57–0.99). 7+ hours (vs <1 hour) per week of unstructured physical activity at age 16, but not age 10, was inversely associated with breast cancer (HR=0.81; 95% CI: 0.70–0.95). Associations were more pronounced for ER+ tumors, especially for activity during the childhood (age 5–12) period. Due to low correlation between childhood/teenage and adulthood activity in this study ($r=0.1$), it is unlikely that recent activity explains our results.

Conclusions—Findings from this large cohort indicate higher levels of physical activity during ages 5–19 are inversely associated with breast cancer risk, supporting early life as a window of susceptibility for breast cancer development.

Keywords

Childhood; early-life; physical activity; breast cancer

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Compliance with Ethical Standards:

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of Institutional Review Boards of the National Institute of Environmental Health Sciences, National Institutes of Health, and the Copernicus Group and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Conflict of interest: The authors declare they have no conflict of interest.

Informed consent: Informed consent was obtained from all individual participants included in the Sister Study.

Introduction

Physical activity is associated with reduced risk of numerous health outcomes, including breast cancer. A meta-analysis of 38 cohort studies reported a relative risk of 0.88 (95% CI: 0.89, 0.90) for breast cancer incidence comparing highest vs. lowest categories of physical activity during adulthood [1]. Evaluating risk factors during childhood and adolescence is of particular interest as early life may be a window of susceptibility due to breast development and hormonal changes [2].

Among studies published to date on childhood and teenage physical activity, a majority have been case-control. Most of the case-control studies reported a decreased risk of breast cancer [3–9], although a few reported no association [10–12]. Results were inconsistent by menopausal status and none examined estrogen receptor (ER) status. In the few cohort studies that have been conducted, results were mixed [13–16]. All cohort studies included only physical activity after age 12. Therefore, it is unknown whether childhood activity before age 12 is associated with decreased breast cancer risk later in life. It is possible that physical activity in childhood or teenage years could contribute to breast cancer risk through different mechanisms. Childhood may precede and be more relevant for early hormonal changes, whereas teenage years may be closer to ductal branching and elongation during breast development [17, 18]. Further, examining both periods may help target prevention and messaging.

The US Department of Health and Human Services' *Physical Activity Guidelines for Americans* recommends children and adolescents get 60 minutes of moderate to vigorous physical activity per day [19]. However, only 24.8% of children and adolescents meet this recommendation [20]. Youth activity increases the chances of a healthy adulthood and lowers the prevalence of risk factors for chronic disease later in life [19]. Given that breast cancer is the most common cancer diagnosed in women in the US, with 252,710 new cases estimated in 2017 [21], it is of public health importance to determine if a modifiable factor such as physical activity decreases breast cancer risk later in life.

The aim of the present study was to evaluate physical activity before age 20 and breast cancer risk, overall and with respect to menopausal and ER status, in a cohort design. We considered hours/week as our primary physical activity metric, but examined MET-hours/week (MET=metabolic equivalent) as an additional classification. We had the unique ability to evaluate these associations for three age periods (childhood: 5–12, teenage: 13–19, and total 5–19).

Materials and Methods

Study Population

The Sister Study is a prospective observational cohort designed to assess environmental risk factors for breast cancer. Study recruitment was conducted from 2003–2009 through media, breast cancer professionals, the Internet, a network of recruitment volunteers, and a national advertising campaign in English and Spanish, which resulted in the enrollment of 50,884

U.S. and Puerto Rican women aged 35–74 at baseline. Eligible participants had a sister who had been diagnosed with breast cancer, but had no prior breast cancer diagnosis themselves.

All participants provided written informed consent and the study was approved by the Institutional Review Boards of the National Institute of Environmental Health Sciences, National Institutes of Health, and the Copernicus Group. The current analysis used Sister Study data release 4.1 with follow-up until July 1st, 2014.

Women completed a computer-assisted telephone interview about family and medical history, lifestyle factors, and demographics at enrollment, subsequent annual health updates, and biennial/triennial follow-up surveys. We excluded 135 women who were diagnosed with breast cancer before their enrollment completed or who were missing date of diagnosis.

Childhood/Teenage Physical Activity Exposures

Childhood and teenage physical activity was assessed during the baseline interview. Participants were asked to report all sports/exercise activities that they did at least once a week for two or more months between ages 5–19. We examined three periods: total (ages 5–19), childhood (ages 5–12), and teenage (ages 13–19). For each activity women reported at what specific ages they did that activity; about how many months per year they did that activity; and in the months they did the activity, about how many hours/week they did the activity. This information was used to calculate the average number of hours/week each year of physical activity, summed across all activities, and divided by the number of years in the period (15 for ages 5–19; 8 for ages 5–12; 7 for ages 13–19). We considered hours/week continuously and categorically. For the categorical variable, we decided *a priori* to use interpretable cut-points: <1, 1–<4, 4–<7, and 7+. These cut-points were chosen so that the <1 hour/week category represents individuals who were mostly inactive; 1–<4 hours/week is equivalent to participating in 1 hour per day less than half of the days per week; 4–<7 hours/week is equivalent to participating in 1 hour per day more than half of the days per week; and 7+ hours/week is equivalent to the US Department of Health and Human Services' physical activity guideline for youth. These cut-points are comparable to another cohort study that examined physical activity during ages 15–18 [16].

Women were additionally asked, “when you were around 10 years old, about how much of your free time did you spend on average each week in physically active play...?” Pre-defined categories were: “< 1 hour”, “at least 1, but less than 3 hours”, “at least 3, but less than 7 hours”, or “7 or more hours/week.” A similar question asked about age 16 unstructured activity.

METs measure intensity of physical activity as the ratio of metabolic rate for a given activity divided by the resting metabolic rate [22]. A compendium of METs for adult activities has been published [22]. All previous papers on youth METs in association with breast cancer used this compendium. However, values determined using adult metabolic rate may not accurately represent intensities for youth [23]. We used an updated compendium of 244 activities for youth [24] to reassign the METs for each activity reported in the Sister Study. In the event that a reported activity was not available in the compendium we equated it to a similar activity or continued to use the previously assigned adult value. Average MET-hours/

week were calculated for the three periods and considered continuously and categorically. For the categorical variable, women who reported no activities were the referent and remaining women were classified into quartiles. The top quartile was split into 75th–<95th and 95th percentile to determine if effects were different with the highest intensity.

Although MET-hours are sometimes considered a better metric than hours/week in studies of adults, in this analysis of childhood/teenage activity we elected to focus primarily on hours/week. Hours/week are more interpretable for public health messaging, and despite updating the compendium, there were still some activities where childhood METs were unknown and adult METs had to be used. Furthermore, in order for researchers to match the proper MET value from the compendium to an activity, characteristics of the activity level (e.g. competitive, strenuous, leisurely) had to have been reported by participants. For example, "competitive basketball games" have a higher value than "basketball, shooting hoops." Some participants may not have distinguished between intensity levels and thus an average score would be assigned. Thus, classification of hours may be less prone to misclassification than MET hours which require information on the intensity of past activities.

Incident Breast Cancer

Participants completed annual health updates and triennial follow-up questionnaires regarding changes in health, lifestyle, and exposures. Women who reported an incident breast cancer diagnosis were asked for medical record release. Response rates were >94% during follow-up [25] and medical records have been obtained for >81% of participants with a breast cancer diagnosis [26]. Agreement was 99% for breast cancer diagnoses and 90% for ER status between medical record and self-report [26]. Therefore, self-report was used when medical records were not available. We report associations for both *in situ* and invasive breast cancers together; in a sensitivity analysis considering invasive cancers alone, results were unchanged.

Statistical Analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined using Cox proportional hazards regression with age as the time scale and person-time accrued from age at enrollment. Follow-up continued until a woman received a breast cancer diagnosis or date of last follow-up. For analyses by ER status, competing or undefined subtypes were censored at date of diagnosis. For example, analyses for ER+ tumors censored women with ER– tumors at diagnosis date. We tested for etiologic heterogeneity by ER status comparing ER+ vs. ER– breast cancer using a logistic model for each exposure variable.

Women were classified as premenopausal if they reported 1 menstrual cycle(s) within the past 12 months. Women who experienced menopause due to hysterectomy (with retention of ovarian tissue) or ovarian suppression medications were classified as premenopausal age 55 and postmenopausal after age 55. In analyses of premenopausal breast cancer, women who transitioned from premenopause to postmenopause during follow-up were censored at the age of menopause. Person-time occurring after menopause only contributed to postmenopausal time at risk.

Potential confounders were determined *a priori* using a directed acyclic graph [27, 28]. Adjusted models included race (non-Hispanic white, non-Hispanic black, Hispanic, other), childhood residence location (urban, suburban, small town, rural, other), family income level while growing up (poor, low income, middle income, well off), highest level of education in the household while growing up (< high school, high school equivalent, some college, 4 year degree), and age 10 fruit and vegetable intake (<1 serving/week, 1–6 servings/week, 1–<2 servings/day, 2+ servings/day). We did not adjust for variables that occurred after age 19 (e.g. parity, adult body mass index, age at menopause, or hormone replacement therapy), which could be mediators. Relative weight at age 10 was considered a confounder or modifier in sensitivity analyses, but results were unchanged so it was left out of final models. Age at menarche could potentially act as either a mediator or a confounder because it may have occurred after childhood, but before teenage activity. Therefore, we examined multiple modeling choices. Results did not differ whether we adjusted for age at menarche in models for any period or did not, when we stratified hours/week of physical activity during the total period by median age at menarche, or when we adjusted for age at menarche in the teenage (age 13–19) model restricted to those with age at menarche <13 years. Results of these various analyses were unchanged from those not adjusted for age at menarche, so it was left out of our final models.

We estimated the Spearman correlation coefficient between continuous total hours/week of physical activity at age 5–19 and adult physical activity at time of study enrollment.

As a sensitivity analysis we stratified associations for age 5–19 hours/week with breast cancer by 10-year birth cohorts to determine if the effects were driven by particular birth years. Another sensitivity analysis evaluated modification by extent of family history (1 vs. 2+ first degree relatives).

The proportional hazards assumption was tested by an interaction term between age and exposure; the assumption was not violated. Missing data was <5% for each covariate (6.4% of women combined) so individuals with missing data were excluded. All tests were two-sided with $\alpha=0.05$. Analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 2,416 breast cancer diagnoses among the 50,749 women and 326,242 person-years at risk. Average follow-up was 6.4 years. Table 1 shows characteristics of the study population stratified by hours/week of physical activity during ages 5–19. Women who participated in 7+ hours/week of sports/exercise activities as youth were more likely to grow up in a household where the highest level of education was college, report a “well off” family income, consume 2+ servings of fruits and vegetables per day at age 10, and classify themselves as lighter than their peers at age 10. There were 343 women missing data on physical activity during ages 5–19, 167 missing age 10 free time active play, and 88 missing age 16 unstructured physical activity.

Associations for hours/week of activity during each age period are shown in Table 2. Individuals who participated in 7+ hours/week of physical activity during ages 5–19 had a reduced risk of breast cancer compared to those with <1 hour/week (HR=0.75; 95% CI: 0.57, 0.99). Inverse associations were suggestive for both childhood and teenage years separately, although they did not reach statistical significance. 7+ hours of unstructured physical activity at age 16 also was associated with reduced breast cancer risk (HR=0.81; 95% CI 0.70, 0.95). Activity during ages 5–19 was not strongly correlated with adult activity ($r=0.1$).

Among the cases, 1,780 had ER+ and 340 had ER– tumors. Inverse associations with hour/week variables were more apparent for ER+ tumors compared to ER– tumors (Table 3), especially during childhood ($p=0.01$, continuous). However, there were fewer ER– cases making the confidence intervals less precise in that subgroup. In childhood, the HR comparing 7+ hours vs. <1 hour of physical activity was 0.63 (95% CI: 0.44, 0.92) for ER+ tumors compared 1.48 (95% CI: 0.83, 2.65) for ER– tumors. Further, inverse associations for ER+ tumors appeared strongest in childhood compared to other periods.

We also found a suggestive reduced risk associated with the highest category (top 5%) of childhood MET-hours/week of sports and exercise activities (HR=0.74; 95% CI: 0.53, 1.03) (Online Resource 1, Supplemental Table 1). The associations differed by ER status for METs in childhood ($p=0.01$, continuous). In the top category of MET-hours/week the HR was 0.58 (95% CI: 0.38, 0.88) for ER+ tumors and 1.68 (95% CI: 0.93, 3.03) for ER– tumors (Online Resource 1, Supplemental Table 2). Consistent with hours/week variables, childhood demonstrated stronger inverse associations for ER+ tumors compared to other periods.

Results for each 1 hour/week increase of physical activity on the continuous scale were generally null, with the exception of inverse associations for ER+ tumors during childhood (Tables 2 and 3). Associations for both hours/week and MET-hours/week with breast cancer did not differ substantially for premenopausal and postmenopausal breast cancer (Online Resource 1, Supplemental Tables 3 and 4). Two exceptions were that the inverse association in the top category of age 16 hours/week of unstructured physical activity and childhood MET-hours/week appeared stronger for premenopausal breast cancer (Online Resource 1, Supplemental Tables 3 and 4), although these were based on fewer numbers. No particular 10-year birth cohort drove the associations and there was no modification by extent of family history (data not shown).

Discussion

In this large cohort study we observed reduced risk of breast cancer for individuals who were very physically active during their adolescence, specifically for exercising 7+ hours/week during ages 5–19 and participating in 7+ hours of unstructured physical activity at age 16. A similar inverse association was found among individuals whose childhood MET-hours/week of physical activity intensity was in the top 5%. Further, the associations appeared stronger in women with ER+ breast cancers, primarily during childhood. Differences by menopausal status were less apparent. In our study, we did not find that

childhood physical activity levels correlated strongly with adult physical activity, suggesting our results are not driven by adult activity.

Our results of a reduced risk of breast cancer in the highest level of physical activity are consistent with most other studies that assessed hours [3, 7], or MET-hours [5–8, 4, 13, 15] of physical activity, although not all [10, 14, 16]. Among cohort studies, Margolis et al. found no association between physical activity measured using a 5-point scale at age 14 and breast cancer in premenopausal women [14]. Peters et al. found no association for hours/week of physical activity during ages 15–18 and postmenopausal breast cancer [16]. The lack of an association found in the Peters et al. study contrasts with our reported inverse associations, which may result from differences in exposure assessment. Their questionnaire was structured so that participants reported the number of hours of “light intensity activities” and “moderate-to-vigorous activities” as a group. Conversely, our study asked women to report specific activities that they participated in, which may have improved recall if it helped women pinpoint specific experiences. Finally, their exposure assessment only asked about physical activity after age 14, whereas our study further includes ages 5–13. It was a benefit of our study to include this childhood period in order to examine a number of windows of susceptibility, but it is potentially prone to more recall error. Significant inverse associations were observed in the Nurses’ Health Study II, although they only reported results for MET-hours of activity. In their study, age 14–22 physical activity was associated with premenopausal, but not postmenopausal, breast cancer for the highest MET category compared to the lowest and there were no consistent differences by ER status [13]. Each reported activity was put into one of three groups: walking, moderate activity, or strenuous activity and then every activity within a group was weighted by the same MET score. On the other hand, we assigned each activity its own MET score and, where possible, used a compendium of MET scores specific for children/adolescents [24].

It is biologically plausible for early life physical activity to be associated with a decreased risk of breast cancer. The childhood and teenage periods included in this study are around the time of puberty, breast development, and hormonal changes which may result in a particularly relevant window of susceptibility. One hypothesized biologic mechanism is that physical activity may delay age at menarche [29] and lead to greater frequency of anovulatory cycles, therefore reducing lifetime cumulative exposure to estrogen, a risk factor for breast cancer [9]. Physical activity during childhood (ages 5–12) may have preceded or occurred around the same time as early hormonal changes. This is consistent with our findings that the inverse associations for ER+ tumors were more pronounced in childhood compared to other periods and that there was a significant difference between ER+ and ER– tumors associated with physical activity in this period. In our population the average age of menarche was 12.6 years, so the childhood (age 5–12) and teenage (age 13–19) periods approximate a stratification by age at menarche.

Physical activity results in other beneficial biologic processes with respect to breast cancer including reduced inflammation and oxidative stress, increased insulin sensitivity, and regulation of body weight and prevention of adiposity, leading to lower levels of adipokines and insulin [30, 31]. Epigenetics may also play an important role; for example, higher physical activity across childhood, teenage years, and the previous 12 months was associated

with altered global methylation of DNA in a manner consistent with the association between physical activity and decreased breast cancer risk [32].

The current study had several strengths. Of importance was the prospective design of the cohort. Women were asked about their childhood and teenage physical activities prior to their diagnosis of breast cancer. Knowledge about disease status could not have differentially influenced recall. Additionally, we assessed physical activity for three periods: total (ages 5–19), childhood (ages 5–12), and teenage (ages 13–19). With one exception [8], previous studies did not collect data or report estimates on physical activity before age 12, a time period that we found to also be of importance, especially for the development of ER+ tumors. The one other study that reported on activity before age 12 was a case-control design that used a relative measure of physical activity [8]. Women were asked whether they were “less active”, “equally active”, or “more active” than their peers at ages 10–12 and at ages 13–15. However, unlike our study, they did not have data on hours/week or MET-hours/week of activity in these periods.

Our study also had some limitations. We cannot exclude the possibility of non-differential exposure misclassification because women were asked to recall physical activity from earlier in life. Since the exposure variables had more than two categories the bias from non-differential misclassification could be in either direction [33]. Results for free play at age 10 and unstructured physical activity at age 16 were seemingly inconsistent. However, the response categories for these questions did not fully capture the range of physical activity at age 10, with nearly 60% of the women reporting 7+ hours of free play. Despite the large overall sample size, there were fewer premenopausal women and ER-tumors. Therefore, estimates in these groups were less stable. Finally, women in the Sister Study cohort have a family history of breast cancer, putting them at a higher risk of breast cancer compared to women without a family history. However, the distribution of breast cancer risk factors in this study population is similar to the general population and suggests that results remain broadly generalizable [34]. We examined associations stratified by extent of family history and found no difference in women who had one first degree relative with breast cancer compared to two or more.

The US Department of Health and Human Services recommends that youth ages 5–17 get at least 60 minutes of physical activity per day [19]. The results of this study of a reduced risk of breast cancer among those who participated in 7+ hours/week of physical activity between ages 5–19 is consistent with this recommendation. However, few children and teenagers are meeting this guideline; as such, strategies to attain this level of activity are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by a National Institute of Environmental Health Sciences training grant to the University of North Carolina (T32ES007018) and by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES044005).

The authors appreciate the helpful comments of Drs. Hazel Nichols and Lawrence Engel.

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Table 1

Characteristics of the study population by age 5–19 physical activity, The Sister Study

	<1 hour per week N=34,193 (68%)		1–6 hours per week N=14,513 (29%)		7+ hours per week N=1,700 (3%)	
	N	%	N	%	N	%
Age at baseline (mean, sd)	56.3	8.7	54.1	9.3	54.3	9.2
Age at menarche (mean, sd)	12.6	1.5	12.7	1.6	12.7	1.8
Race/Ethnicity						
Non-Hispanic white	28,459	83.2	12,304	84.8	1,404	82.6
Non-Hispanic black	2,963	8.7	1,282	8.8	172	10.1
Hispanic	1,912	5.6	517	3.6	65	3.8
Other	854	2.5	407	2.8	58	3.4
Highest education in the household at age 13						
Less than high school	7,151	21.2	1,848	12.8	233	13.8
High school graduate	12,462	37.0	4,856	33.7	517	30.7
Some college	6,223	18.5	2,868	19.9	329	19.5
College degree or higher	7,892	23.4	4,840	33.6	607	36.0
Family income while growing up						
Poor	3,056	9.0	859	5.9	114	6.8
Low income	9,619	28.2	3,090	21.3	338	20.0
Middle income	19,773	57.9	9,242	63.8	1,015	60.1
Well off	1,680	4.9	1,292	8.9	222	13.1
Residence type						
Urban	7,924	23.5	3,002	20.9	390	23.3
Suburban	8,958	26.5	4,446	30.9	480	28.6
Small town	8,421	25.0	3,950	27.5	460	27.4
Rural	8,363	24.8	2,950	20.5	341	20.3
Other	87	0.3	39	0.3	6	0.4
Smoked before age 20						
No	22,876	66.9	9,540	65.7	1,082	63.7
Yes	11,311	33.1	4,972	34.3	617	36.3

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	<1 hour per week N=34,193 (68%)		1–6 hours per week N=14,513 (29%)		7+ hours per week N=1,700 (3%)	
	N	%	N	%	N	%
Age 10 fruit and vegetable intake						
<1 serving per week	282	0.9	54	0.4	4	0.3
1–6 servings per week	4,831	14.7	1,474	10.6	158	9.9
1–<2 servings per day	14,383	43.6	5,503	39.5	532	33.2
2+ servings per day	13,464	40.9	6,886	49.5	908	56.7
Relative weight to peers at age 10						
Lighter	11,680	34.3	5,239	36.2	690	40.7
Same	16,072	47.2	6,693	46.2	760	44.8
Heavier	6,323	18.6	2,556	17.6	246	14.5

HRs and 95% CIs for associations of hours/week physical activity during childhood/teens with breast cancer overall, The Sister Study

Table 2

	PY (N=326,465)	N cases (N=2,416)	HR ^a (95% CI)
Hours/week total (age 5–19)			
Continuous	324,184	2,398	0.99 (0.97, 1.01)
0–<1	220,076	1,636	1
1–<4	74,440	553	1.03 (0.93, 1.13)
4–<7	18,888	146	1.08 (0.91, 1.29)
7+	10,779	63	0.75 (0.57, 0.99)
Hours/week child (age 5–12)			
Continuous	324,184	2,398	0.99 (0.97, 1.01)
0–<1	251,615	1,864	1
1–<4	50,536	389	1.06 (0.94, 1.19)
4–<7	13,372	90	0.92 (0.74, 1.15)
7+	8,660	55	0.80 (0.59, 1.07)
Hours/week teens (age 13–19)			
Continuous	324,184	2,398	0.99 (0.98, 1.01)
0–<1	203,288	1,513	1
1–<4	76,090	589	1.06 (0.96, 1.17)
4–<7	25,422	170	0.93 (0.78, 1.09)
7+	19,384	126	0.88 (0.72, 1.07)
Hours/week age 10 free time active play			
0–<1	8,576	64	1
1–<3	37,256	261	1.01 (0.75, 1.35)
3–<7	87,929	683	1.11 (0.84, 1.47)
7+	191,531	1,395	1.10 (0.84, 1.44)
Hours/week age 16 unstructured physical activity			
0–<1	71,933	539	1
1–<3	115,784	885	1.01 (0.90, 1.13)
3–<7	93,918	715	0.99 (0.88, 1.11)
7+	44,083	271	0.81 (0.70, 0.95)

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Abbreviations: HR, hazard ratio; CI, confidence interval; PY, person-years; N, number

^a Adjusted for race, urban/rural childhood residence, family income while growing up, highest education in household growing up, age 10 fruit and vegetable intake

HRs and 95% CIs for associations of hours/week physical activity with ER+ and ER– breast cancer, The Sister Study

Table 3

	ER+		ER–		<i>p</i> -value ^b
	N cases	HR ^a (95% CI)	N cases	HR ^a (95% CI)	
Hours/week total (age 5–19)					
Continuous	1,780	0.98 (0.95, 1.00)	340	1.02 (0.98, 1.07)	0.06
0<1	1,224	1	235	1	
1<4	403	0.99 (0.88, 1.11)	73	0.97 (0.74, 1.27)	
4<7	107	1.07 (0.87, 1.31)	23	1.14 (0.73, 1.79)	
7+	46	0.69 (0.50, 0.96)	9	0.87 (0.45, 1.70)	1.0
Hours/week child (age 5–12)					
Continuous	1,780	0.97 (0.94, 0.99)	340	1.04 (0.99, 1.08)	0.01
0<1	1,406	1	256	1	
1<4	271	0.96 (0.84, 1.10)	57	1.17 (0.87, 1.56)	
4<7	68	0.93 (0.72, 1.19)	15	1.04 (0.60, 1.83)	
7+	35	0.63 (0.44, 0.92)	12	1.48 (0.83, 2.65)	0.1
Hours/week teens (age 13–19)					
Continuous	1,780	0.99 (0.97, 1.00)	340	1.01 (0.97, 1.05)	0.4
0<1	1,133	1	217	1	
1<4	438	1.05 (0.94, 1.18)	83	1.08 (0.83, 1.40)	
4<7	115	0.82 (0.67, 1.01)	23	0.89 (0.57, 1.38)	
7+	94	0.87 (0.69, 1.09)	17	0.86 (0.52, 1.44)	1.0
Hours/week age 10 free time active play					
0<1	46	1	9	1	
1–2	199	0.99 (0.70, 1.38)	30	0.94 (0.41, 2.14)	
3–6	522	1.09 (0.79, 1.50)	90	1.15 (0.53, 2.50)	
7+	1,016	1.02 (0.74, 1.39)	211	1.25 (0.58, 2.67)	0.4
Hours/week age 16 unstructured physical activity					
0<1	410	1	69	1	
1–2	649	0.96 (0.84, 1.09)	129	1.22 (0.91, 1.65)	
3–6	527	0.97 (0.85, 1.10)	107	1.16 (0.85, 1.59)	

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ER+		ER–		p-value ^b
N cases	HR ^a (95% CI)	N cases	HR ^a (95% CI)	
7+	203	36	0.88 (0.58, 1.34)	0.5

Abbreviations: HR, hazard ratio; CI, confidence interval; ER, estrogen receptor; +, positive; –, negative

^a Adjusted for race, urban/rural childhood residence, family income level while growing up, highest education in household growing up, age 10 fruit and vegetable intake

^b Test of heterogeneity, using a logistic model comparing ER+ vs. ER– tumors