Published OnlineFirst August 7, 2014; DOI: 10.1158/1055-9965.EPI-14-0448

Cancer Epidemiology, Biomarkers & Prevention

Research Article

A Prospective Study of Physical Activity and Breast Cancer Incidence in African-American Women

Lynn Rosenberg[1], Julie R. Palmer[1], Traci N. Bethea[1], Yulun Ban[1], Kristen Kipping-Ruane[1], and Lucile L. Adams-Campbell[2]

Abstract

Background: Physical activity has been associated with reduced risk of breast cancer. Evidence on the association in African Americans is limited.

Methods: With prospective data from the Black Women's Health Study, we assessed vigorous exercise and walking in relation to incidence of invasive breast cancer overall ($n = 1,364$), estrogen receptor–positive (ER^+, $n = 688$) cancer, and estrogen receptor–negative (ER^-, $n = 405$) cancer, based on 307,672 person-years of follow-up of 44,708 African-American women ages 30 years or older at enrollment. Cox proportional hazards models estimated incidence rate ratios (IRR) and 95% confidence intervals (CI).

Results: Vigorous exercise at baseline was inversely associated with overall breast cancer incidence ($P_{trend} = 0.05$): the IRR for ≥7 h/wk relative to <1 h/wk was 0.74 (95% CI, 0.57–0.96). The association did not differ by ER status. Brisk walking for ≥7 h/wk was associated with a reduction similar to that for vigorous exercise. Vigorous exercise at the age of 30 years, 21 years, or in high school was not associated with breast cancer incidence. Sitting for long periods at work or watching TV was not significantly associated with breast cancer incidence.

Conclusion: High levels of vigorous exercise or brisk walking may be associated with a reduction in incidence of breast cancer in African-American women.

Impact: These results provide informative data on a potential modifiable risk factor, exercise, for breast cancer in African-American women. *Cancer Epidemiol Biomarkers Prev; 23(11); 2522–31. ©2014 AACR.*

Introduction

Many studies, mostly of white women, have found associations of various types of physical activity with reduced risk of breast cancer (1–5). The World Cancer Research Fund/American Institute for Cancer Research expert panel concluded in 2007 that an inverse association of physical activity with postmenopausal breast cancer was probable (4), based on evidence from both follow-up and case–control studies. Their conclusion on premenopausal breast cancer was that there was limited evidence for an inverse association. With the addition of newly reported studies, their conclusions in 2010 were unchanged; for premenopausal breast cancer, in particular, the evidence from follow-up studies was judged to be inconsistent, whereas that from case–control studies suggested an inverse association (5). The optimal type of physical activity, time period, and amount of activity are not established. In a meta-analysis of 31 prospective studies of physical activity and breast cancer that assessed a variety of activity measures, an overall reduction in risk of approximately 12% was estimated for the highest level of recreational physical activity relative to the lowest, and associations were strongest for vigorous recreational activity (6).

The results of the few studies of physical activity and breast cancer among African-American women are inconsistent (7–11). Data on physical activity in relation to molecular subtype of breast cancer are also sparse and inconsistent (7, 12–19). Whether physical activity reduces incidence of estrogen receptor (ER)-negative breast cancer is of particular interest because this subtype has a worse prognosis than ER^+ cancer (20) and disproportionately affects African-American women (20–22).

In the present study, we prospectively assessed vigorous exercise at baseline, 30 years of age or 21 years, and in high school in relation to incidence of breast cancer overall and by estrogen receptor status in African-American women. We also assessed time spent brisk walking, sitting watching television, and sitting at work. The data were obtained during 16 years of follow-up in the Black Women's Health Study (BWHS), a cohort study established in 1995. In an early cross-sectional analysis, vigorous exercise was inversely associated with prevalent breast cancer (23).

[1]Slone Epidemiology Center, Boston University, Boston, Massachusetts. [2]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, District of Columbia.

Corresponding Author: Lynn Rosenberg, Slone Epidemiology Center at Boston University, 1010 Commonwealth Avenue, Boston, MA 02215. Phone: 617-734-6006; Fax: 617-738-5119; E-mail: lrosenbe@bu.edu

doi: 10.1158/1055-9965.EPI-14-0448

Published OnlineFirst August 7, 2014; DOI: 10.1158/1055-9965.EPI-14-0448

Materials and Methods

The BWHS

The BWHS is an ongoing follow-up study that began in 1995 when 59,000 African-American women aged 21–69 years from the mainland United States enrolled by completing mailed health questionnaires. The women provided information on demographic characteristics, weight, height, recreational exercise, medical history, and other factors. They are followed every 2 years through mailed and web questionnaires that update exposure information and ascertain incident breast cancer and other outcomes (24). Deaths are ascertained through family members, the U.S. Postal service, and the National Death Index. Follow-up of the baseline cohort over 7 completed questionnaire cycles is 80%. The Boston University Medical Campus Institutional Review Board approved the research.

Physical activity

At baseline in 1995, participants reported the average number of hours per week (none, <1, 1, 2, 3–4, 5–6, 7–9, ≥10) spent in vigorous physical activity (e.g., basketball, swimming, running, aerobics) at baseline (in the previous year), at around the age of 30 years and 21 years, and in high school. They reported hours per week of walking for exercise at baseline (none, <1, 1, 2, 3–4, 5–6, 7–9, ≥10), and in 2003 and 2005, they reported the pace of walking (stroll, <2 mph; average, 2–3 mph; fairly brisk, 3–4 mph; brisk, ≥4 mph). A participant's walking was defined as brisk if she reported on the 2003 or 2005 questionnaire that her pace of walking was fairly brisk or brisk. Vigorous activity and walking for exercise were updated on follow-up questionnaires in 1997, 1999, 2001, and 2009. Hours per day spent sitting watching television (0, <1, 1–2, 3–4, ≥5 h/d) and sitting at work (0, <1, 1–2, 3–4, ≥5 h/d) was asked in 1995 and updated in 1997, 1999, and 2001. In a validation study in which participants wore actigraphs (activity monitors) during their waking hours for a week, actigraph counts were significantly correlated with BWHS questionnaire data on recent vigorous exercise ($r = 0.40$, $P < 0.05$; ref. 25).

Covariates

The baseline questionnaire collected information on adult height, current weight, age at menarche, parity, age at first birth, breast cancer in first-degree relatives, alcohol consumption, cigarette smoking, menopausal status, age at menopause, oral contraceptive use, use of menopausal female hormone supplements, and years of education. It also collected data on usual diet in the past year with a 68-item version of the National Cancer Institute-Block food frequency questionnaire.(26) Follow-up questionnaires updated information on weight, alcohol consumption, parity, menopausal status, age at menopause, oral contraceptive use, supplemental female hormone use, years of education, and dietary intake. As described previously (27), factor analysis was used to identify 2 major dietary patterns based on 35 foods or food groups from the food frequency questionnaire data: the "vegetables/fruit" pattern (sometimes called "prudent") was characterized by high intake of fruits and vegetables, and the "meat/fried foods" pattern (sometimes called "Western") was characterized by high intake of meat, fried foods, and sweets. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Breast cancer cases

Incident breast cancers were ascertained largely through self-report on the biennial follow-up questionnaires, and a small proportion was ascertained through linkage to 24 state cancer registries in the states in which 95% of BWHS participants reside. Confirmation was through hospital pathology records and pathology data from the cancer registries. Of cases for which pathology records have been obtained to date (>80%), more than 99% were confirmed. The present analysis is based on 1,364 confirmed invasive breast cancer cases ascertained through year 2011 among women who were aged 30 years or older at baseline; 8.0% of cases were diagnosed at 30–39 years, 32.4% at 40–49 years, 35.2% at 50–59 years, and 24.4% at 60 years or older. Information on hormone receptor status was available for 80% of the cases, of which 688 were classified as ER^+ and 405 as ER^-; among the latter, pathology data were sufficient to classify 137 as triple-negative [ER^-/progesterone receptor $(PR)^-$/$HER2^-$]. The distribution of ER and PR status was similar to that reported elsewhere for African-American women (28–30). Breast cancer risk factors were similar in cases with known and unknown receptor status (31, 32).

Statistical analysis

Very few breast cancer cases occurred among women younger than 30 years. We confined the analysis to women 30 years or older at baseline and excluded 1,273 women who reported having had cancer and 838 women who did not report their vigorous exercise on the baseline questionnaire, resulting in an analytic cohort of 44,078 women. We used Cox proportional hazards models to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) for the association of categories of vigorous exercise, walking, and sitting with incidence of breast cancer. In the analysis of brisk walking, hours of walking at a pace slower than fairly brisk or brisk was assigned a value of 0 h/wk of brisk walking. Participants contributed person time to the analysis from baseline until the occurrence of breast cancer, loss to follow-up (the date of the last returned questionnaire), death, or the end of follow-up in 2011, whichever occurred first. Ductal carcinoma *in situ* breast cancer cases were censored at the date of diagnosis. From 1995 through 2011, a total of 307,672 person years were accumulated.

For vigorous exercise at 4 time points (baseline, 30 years, 21 years, and high school), we assessed exercise in that period relative to <1 h/wk of exercise in that period. In a time-varying analysis, we updated vigorous exercise during follow-up. In an analysis of the sum of metabolic equivalent hours (MET-h) from vigorous exercise and

Published OnlineFirst August 7, 2014; DOI: 10.1158/1055-9965.EPI-14-0448

brisk walking (defined as fairly brisk or brisk walking), we assigned 6 METs to each hour of vigorous exercise and 3.5 METs to each hour of brisk walking (33). We assessed sitting at work and sitting watching TV both at baseline and as time varying. Covariates that changed over time (e.g., BMI) were treated as time-varying in the analyses; the Andersen–Gill data structure was used to update these covariates and exact methods were used to handle tied events (34). The multivariable models were adjusted for the factors most strongly associated with exercise in our data: age (single year), time period (questionnaire cycle), BMI (<25, 25–29, ≥30), parity (0, 1, 2, ≥3), years of education (≤12, 13–15, 16, ≥17), vegetable/fruit dietary pattern (quintiles), and meat/fried foods dietary pattern (quintiles). The analyses of brisk walking were adjusted, in addition, for vigorous exercise, and the analyses of sitting at work and sitting watching TV were adjusted for vigorous exercise and mutually for each other. Models that further controlled for age at menarche, age at first birth, oral contraceptive use, supplemental female hormone use, menopausal status, age at menopause, history of breast cancer in a first-degree relative, alcohol consumption, and cigarette smoking yielded IRR estimates that were within 2% of the estimates from the restricted model that controlled for age, time period, BMI, parity, education, and dietary pattern; only the latter estimates are presented. In addition, the multivariable IRRs were closely similar to estimates from models in which only age and calendar time were controlled. Tests for trend were conducted by using an ordinal value for each level of exercise modeled as a single variable. Tests for interaction were performed using the likelihood ratio test comparing models with and without cross-product terms between the covariate and physical activity. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc.).

Results

Relative to women who exercised vigorously <1 h/wk at baseline (Table 1), women who exercised vigorously at least 5 h/wk were younger, more likely to be nulliparous, thinner, more educated, have a dietary pattern high in vegetables and fruits, and less likely to have a dietary pattern low in meats and fried foods. Vigorous exercisers also reported more hours of exercise at 30 years, 21 years, and in high school than less active women and they walked more at baseline. Vigorous exercisers did not differ materially from less active women in hours spent sitting watching TV or sitting at work.

The incidence of breast cancer decreased with increasing hours per week of baseline vigorous exercise ($P_{\mathrm{trend}} = 0.05$; Table 2). IRRs for 5 to 6 h/wk and ≥7 h/wk relative to <1 h/wk were 0.89 (95% CI, 0.69–1.14) and 0.74 (95% CI, 0.57–0.96), respectively. For ER^+ breast cancer, the IRR for ≥7 h/wk relative to <1 h/wk was 0.75 (95% CI, 0.52–1.09; $P_{\mathrm{trend}} = 0.28$), and the corresponding estimate for ER^- breast cancer was 0.85 (95% CI, 0.55–1.33; $P_{\mathrm{trend}} = 0.48$). For triple-negative breast cancer, all IRRs were close to the null, with the IRR for ≥7 h/wk relative to <1 h/wk equal to 0.96 (95% CI, 0.46–2.01). The results were closely similar after additional control for brisk walking and sitting at work and watching TV. Associations were not stronger when vigorous exercise was assessed as a time varying variable.

There were no trends in the IRR estimates across increasing hours per week of vigorous exercise at 30 years, 21 years, or in high school: for ≥7 h/wk relative to <1 h/wk, the IRR was 1.00 (95% CI, 0.82–1.24) for exercise at 30 years of age, 1.09 (95% CI, 0.92–1.31) for exercise at 21 years of age, and 1.01 (95% CI, 0.84–1.20) for exercise during high school. In an analysis that assessed an average of vigorous exercise reported at baseline, 30 years, 21 years, and in high school, the IRRs were close to 1.0. Many women varied considerably in their exercise habits over time despite the correlation of recent exercise with exercise in earlier life. To assess the most consistent exercisers, we restricted an analysis to women who reported at least 5 h/wk of vigorous exercise in every time period (baseline, 30 years, 21 years, and high school) and women who reported <1 h/wk of vigorous exercise in every time period. On the basis of 45 incident breast cancer cases that occurred among women in the ≥5 h/wk stratum and 112 that occurred in the <1 h/wk stratum, the IRR for breast cancer overall was 0.70 (95% CI, 0.58–1.06); the corresponding estimates were 0.84 (95% CI, 0.56–1.27) for ER^+ cancer (based on 24 and 55 cases, respectively) and 0.66 (95% CI, 0.37–1.18) for ER^- breast cancer (based on 12 and 37 cases, respectively).

Walking for exercise at baseline without taking account of pace was not associated with incidence of breast cancer: the IRR for ≥7 h/wk relative to <1 h/wk was 0.98 (95% CI, 0.77–1.23) for breast cancer overall, 0.99 (95% CI, 0.71–1.38) for ER^+ cancer, and 0.96 (95% CI, 0.63–1.49) for ER^- cancer. However, as shown in Table 3, brisk walking for exercise at baseline was inversely associated with overall breast cancer incidence ($P_{\mathrm{trend}} < 0.02$) in an analysis that controlled for vigorous exercise: the IRR for ≥7 h/wk relative to <1 h/wk was 0.77 (95% CI, 0.53–0.1.13). The corresponding estimates were 0.83 (95% CI, 0.50–1.38) for ER^+ cancer and 0.88 (95% CI, 0.46–1.68) for ER^- breast cancer. After controlling for sitting watching TV in addition to the other risk factors, the estimates were little changed.

In an analysis of the sum of MET-h from vigorous exercise and brisk walking at baseline, an inverse association with breast cancer incidence was similar to that for vigorous exercise and brisk walking alone: the IRR for ≥45 MET-h/wk relative to none was 0.72 (95% CI, 0.57–0.90) for breast cancer overall, 0.68 (95% CI, 0.50–0.95) for ER^+ cancer, and 0.90 (95% CI, 0.62–1.32) for ER^- cancer.

Associations of baseline vigorous exercise with overall breast cancer incidence within categories of age at diagnosis, BMI, parity, family history of breast cancer, and menopausal status are shown in Table 4. An inverse association was weaker among women who were at least 50 years old than among younger women, but the *P* value for interaction was 0.44. Inverse associations of exercise

Published OnlineFirst August 7, 2014; DOI: 10.1158/1055-9965.EPI-14-0448

Table 1. Vigorous exercise at baseline according to baseline characteristics (age-standardized)

	H/wk		
Characteristics	**<1**	**1–4**	**≥5**
Number of women	22,760	14,638	5,399
Age, %			
30–39	37	51	54
40–49	37	34	33
50–59	18	12	10
≥60	8	3	3
BMI, mean	29.4	27.6	26.7
≥16 years of education, %	40	51	48
Age at menarche ≤ 11, %	28	27	26
Nulliparous, %	24	29	30
First birth before age 20, %	27	22	25
Recent oral contraceptive user, %	32	33	33
Female hormone user, %	19	20	19
Premenopausal, %	70	71	71
Age at menopause < 45, %	21	20	20
Family history of breast cancer, %	7	7	8
Cigarette smoking, %			
Never smoked	58	60	58
<20 pack years	30	31	31
≥20 pack years	10	8	8
Alcohol consumption, %			
Never drank	58	56	55
<7 drinks/d	35	37	36
≥7 drinks/d	6	6	8
Vegetable/fruit pattern, top quintile, %	15	25	33
Meat/fried foods pattern, top quintile, %	23	16	13
Any walking for exercise at baseline			
<1 h/wk	57	27	20
≥5 h/wk	8	13	41
Brisk walking for exercise at baseline			
<1 h/wk	87	71	64
≥5 h/wk	3	6	19
Vigorous exercise at age 30			
≥5 h/wk	9	19	60
Vigorous exercise at age 21			
≥5 h/wk	18	32	53
Vigorous exercise in high school			
≥5 h/wk	28	45	62
Sitting watching TV at baseline			
<1 h/d	10	13	13
≥5 h/d	17	11	15
Sitting at work at baseline			
<1 h/d	20	16	18
≥5 h/d	48	50	50

with breast cancer incidence were similar across strata of BMI, parity, family history of breast cancer and menopausal status.

IRRs for breast cancer for women who reported the most sitting at work or watching TV were slightly above 1.0 (Table 5); these analyses mutually controlled each type of sitting and for vigorous exercise in addition to the other breast cancer risk factors. For breast cancer overall, the IRR was 1.13 (95%, CI 0.91–1.40; $P_{\text{trend}} = 0.66$) for ≥5 h/d of sitting watching TV relative to < 1 h/d, and the corresponding estimate was 1.05 (95% CI, 0.90–1.22) for sitting at work. In a time-varying analysis, the associations were similar. In an analysis in which hours per week of sitting at work and watching television were combined, the IRR for

Published OnlineFirst August 7, 2014; DOI: 10.1158/1055-9965.EPI-14-0448

Table 2. Vigorous exercise at baseline in relation to incidence of breast cancer overall and ER+ and ER− breast cancer

	All breast cancer			ER+ breast cancer		ER− breast cancer	
h/wk	Cases	Person-years	IRR[a] (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)
<1	773	313,900	1.00 (Ref.)	382	1.00 (Ref.)	228	1.00 (Ref.)
1	117	62,939	0.85 (0.70–1.03)	59	0.86 (0.66–1.14)	35	0.83 (0.58–1.18)
2	149	67,081	0.99 (0.83–1.19)	76	1.00 (0.78–1.29)	45	1.00 (0.72–1.38)
3–4	159	77,243	0.94 (0.79–1.12)	84	0.98 (0.77–1.25)	45	0.88 (0.63–1.22)
5–6	69	35,793	0.89 (0.69–1.14)	36	0.92 (0.65–1.30)	23	0.97 (0.63–1.50)
≥7	63	39,593	0.74 (0.57–0.96)	32	0.75 (0.52–1.09)	22	0.85 (0.55–1.33)
			$P_{trend} = 0.05$		$P_{trend} = 0.28$		$P_{trend} = 0.43$

[a]IRRs adjusted for age (single year), time period (questionnaire cycle), years of education (≤12, 13–15, 16, ≥17), parity (0, 1, 2, ≥3), vegetable/fruit dietary pattern (quintiles), and meat/fried foods dietary pattern (quintiles)

breast cancer for ≥10 h/wk relative to <3 h/wk was 1.05 (95% CI, 0.86–1.17).

We assessed the joint effects of vigorous exercise with combined hours of sitting watching TV and at work (Table 6). For breast cancer overall, the IRR estimates were largest for women who exercised vigorously <1 h/wk, intermediate for those who exercised 1–4 h/wk, and lowest for those who exercised at least 5 h/wk, regardless of their hours of sitting. Within these categories of exercise, there were no clear trends in risk across increasing amount of sitting.

Discussion

In this prospective study of African-American women, recent vigorous exercise reported at baseline was inversely associated with overall incidence of breast cancer. The IRRs were close to the null for levels of exercise up to about 5 h/wk, and the estimated reductions in incidence for 5–6 and ≥7 h/wk of exercise were 11% and 26%, respectively. Brisk walking at baseline was associated with similar reductions. If the associations are real, a considerable amount of vigorous exercise or brisk walking is required for a reduction in breast cancer risk. We found no association of vigorous exercise at 30 years, 21 years, or in high school with breast cancer incidence. These variables might have been reported less accurately than recent exercise, or exercise in those time periods may not be relevant. Results from an analysis confined to the relatively small subset of women whose exercise habits were consistent across all time periods did not suggest an inverse association stronger than that for recent exercise.

While there is growing evidence that physical activity is protective against breast cancer (1–5), there are inconsistencies, probably due, in part, to the fact that associations have generally been weak. Even results on vigorous exercise, for which associations have tended to be strongest, have varied, with some studies finding associations for exercise in early life, some for later life, and yet others for exercise throughout the life span (1–6).

Previous results on exercise and breast cancer incidence specifically among African-American women come from

Table 3. Brisk walking at baseline in relation to breast cancer overall, ER+, and ER− breast cancer

	All breast cancer			ER+ breast cancer		ER− breast cancer	
h/wk	Cases	Person-years	IRR[a] (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)
<1	1,086	470,638	1.00 (Ref.)	544	1.00 (Ref.)	310	1.00 (Ref.)
1	67	31,643	0.96 (0.75–1.22)	36	1.02 (0.72–1.43)	23	1.10 (0.72–1.68)
2	59	32,662	0.79 (0.61–1.03)	34	0.88 (0.62–1.25)	14	0.63 (0.37–1.08)
3–4	78	37,884	0.88 (0.69–1.11)	36	0.77 (0.55–1.09)	30	1.17 (0.79–1.71)
5–6	40	20,299	0.84 (0.61–1.16)	20	0.80 (0.51–1.27)	16	1.14 (0.68–1.90)
7+	29	17,057	0.77 (0.53–1.13)	16	0.83 (0.50–1.38)	10	0.88 (0.46–1.68)
			$P_{trend} = 0.02$		$P_{trend} = 0.08$		$P_{trend} = 0.98$

NOTE: Walking defined as brisk based on fairly brisk or brisk pace reported on the 2003 or 2005 questionnaire
[a]IRRs adjusted for age (single year), time period (questionnaire cycle), BMI (<25, 25–29, ≥30 kg/m^2), years of education (≤12, 13–15, 16, ≥17), parity (0, 1, 2, ≥3), vegetable/fruit dietary pattern (quintiles), meat/fried foods dietary pattern (quintiles), and vigorous exercise (<1, 1–4, ≥5 h/wk).

Table 4. Vigorous exercise at baseline in relation to incidence of breast cancer by age, BMI, parity, family history of breast cancer, menopausal status, and age

h/wk	Cases	IRR[a] (95% CI)	Cases	IRR (95% CI)	$P_{interaction}$
	Age < 50		Age ≥ 50		
<1	287	1.00 (Ref.)	486	1.00 (Ref.)	
1	55	0.77 (0.58–1.03)	62	0.90 (0.69–1.18)	
2	63	0.84 (0.64–1.11)	86	1.12 (0.88–1.41)	
3–4	75	0.83 (0.64–1.08)	84	1.02 (0.80–1.29)	
5–6	31	0.74 (0.51–1.08)	38	1.02 (0.73–1.43)	
≥7	26	0.57 (0.38–0.86)	37	0.91 (0.65–1.27)	
		$P_{trend} = 0.003$		$P_{trend} = 0.98$	0.44
	BMI < 30		BMI ≥ 30		
<1	418	1.00 (Ref.)	350	1.00 (Ref.)	
1	71	0.86 (0.67–1.11)	45	0.83 (0.61–1.13)	
2	101	1.09 (0.88–1.36)	48	0.85 (0.62–1.15)	
3–4	110	0.98 (0.79–1.21)	49	0.88 (0.65–1.19)	
5–6	50	0.96 (0.71–1.30)	18	0.74 (0.46–1.19)	
≥7	41	0.73 (0.53–1.01)	22	0.81 (0.52–1.25)	
		$P_{trend} = 0.24$		$P_{trend} = 0.08$	0.28
	Nulliparous		Parous		
<1	137	1.00 (Ref.)	636	1.00 (Ref.)	
1	19	0.69 (0.40–1.04)	98	0.90 (0.73–1.12)	
2	29	0.82 (0.54–1.23)	120	1.05 (0.86–1.28)	
3–4	48	1.12 (0.80–1.59)	111	0.87 (0.71–1.07)	
5–6	16	0.79 (0.46–1.34)	53	0.92 (0.69–1.23)	
≥7	18	0.70 (0.48–1.31)	45	0.72 (0.53–0.97)	
		$P_{trend} = 0.55$		$P_{trend} = 0.05$	0.26
	Family history: yes		Family history: no		
<1	123	1.00 (Ref.)	650	1.00 (Ref.)	
1	16	0.73 (0.43–1.24)	101	0.87 (0.70–1.07)	
2	23	1.04 (0.66–1.64)	126	0.99 (0.82–1.20)	
3–4	28	1.05 (0.68–1.60)	131	0.91 (0.75–1.11)	
5–6	11	0.88 (0.47–1.65)	58	0.89 (0.68–1.17)	
≥7	10	0.75 (0.39–1.44)	53	0.74 (0.56–0.99)	
		$P_{trend} = 0.59$		$P_{trend} = 0.05$	0.97
	Premenopausal		Postmenopausal		
<1	238	1.00 (Ref.)	425	1.00 (Ref.)	
1	52	0.88 (0.65–1.19)	47	0.81 (0.60–1.09)	
2	63	0.99 (0.75–1.31)	65	1.01 (0.78–1.31)	
3–4	74	0.99 (0.76–1.29)	65	0.94 (0.72–1.22)	
5–6	32	0.89 (0.61–1.30)	27	0.85 (0.60–1.33)	
≥7	24	0.64 (0.42–0.98)	32	0.94 (0.66–1.36)	
		$P_{trend} = 0.13$		$P_{trend} = 0.55$	0.76

[a]IRRs adjusted for age (single year), questionnaire cycle, years of education (≤12, 13–14, 16, ≥17), parity (0, 1, 2, ≥3), vegetable/fruit dietary pattern (quintiles), and meat/fried foods dietary pattern (quintiles).

4 case–control studies and a follow-up study. In the Women's Contraceptive and Reproductive Experiences Study (CARE; ref. 7), lifetime recreational physical activity was inversely associated with breast cancer incidence, with an OR of 0.75 (95% CI, 0.61–0.93) for ≥3 h/wk relative to inactivity based on 1,605 African-American cases; the study found no differences by menopausal status. Breast cancer risk was inversely associated with lifetime physical

Table 5. Sitting watching TV and sitting at work in 1995 in relation to incidence of breast cancer overall and ER$^+$ and ER$^-$ breast cancer

	All breast cancer			ER$^+$ breast cancer		ER$^-$ breast cancer	
h/d	Cases	Person-years	IRR[a] (95% CI)	Cases	IRR (95% CI)	Cases	IRR (95% CI)
TV							
<1	158	72,748	1.00 (Ref.)	84	1.00 (Ref.)	43	1.00 (Ref.)
1–2	540	236,342	1.05 (0.88–1.26)	288	1.06 (0.83–1.35)	161	1.18 (0.84–1.65)
3–4	430	206,362	0.97 (0.80–1.16)	212	0.90 (0.70–1.17)	128	1.09 (0.77–1.55)
5+	205	86,367	1.13 (0.91–1.40)	88	0.94 (0.69–1.28)	67	1.39 (0.94–2.07)
			$P_{trend} = 0.66$		$P_{trend} = 0.25$		$P_{trend} = 0.24$
Work							
<1	260	110,837	1.00 (Ref.)	136	1.00 (Ref.)	71	1.00 (Ref.)
1–2	164	70,811	1.06 (0.87–1.30)	89	1.06 (0.80–1.39)	48	1.10 (0.76–1.60)
3–4	257	105,176	1.15 (0.96–1.37)	146	1.19 (0.94–1.52)	56	0.89 (0.62–1.27)
5+	635	301,221	1.05 (0.90–1.22)	294	0.92 (0.74–1.13)	211	1.19 (0.90–1.57)
			$P_{trend} = 0.68$		$P_{trend} = 0.26$		$P_{trend} = 0.21$

[a]IRRs adjusted for age (single year), time period (questionnaire cycle), BMI (<25, 25–29, ≥30 kg/m^2), years of education (≤12, 13–15, 16, ≥17), parity (0, 1, 2, ≥3), vegetable/fruit dietary pattern (quintiles), meat/fried foods dietary pattern (quintiles), and vigorous activity; sitting watching TV adjusted for sitting at work and vice versa.

activity in premenopausal and postmenopausal women in a case–control study in San Francisco that included 394 African-American cases (9) and with recent exercise in 2 case–control studies that included 88 African-American cases from one study (10) and 97 African-American cases from the other (11). The only previous findings specific to African-American women based on prospectively collected data come from the Southern Community Cohort follow-up study: based on a nested case–control study composed largely of postmenopausal women that included 374 African-American cases, neither recreational activity at baseline nor at ages 30–39 years was significantly associated with breast cancer risk (8).

We found no evidence that the association of baseline physical activity with breast cancer incidence differed by ER status, but larger numbers will be required to firmly establish whether there are differences. In 2 studies that found inverse associations of physical activity with breast cancer overall, the inverse associations have been stronger for ER$^-$ cancer: in the California Teachers follow-up study, average lifetime exercise was not associated significantly with incidence of ER$^+$ breast cancer (based on 1,879 cases), whereas there was a statistically significant inverse association with ER$^-$ cancer (345 cases; ref. 14); the association was present among postmenopausal women, and the number of premenopausal cases was insufficient

Table 6. Vigorous exercise together with combined sitting watching TV and sitting at work in 1995 in relation to incidence of breast cancer overall and ER$^+$ and ER$^-$ breast cancer

		All breast cancer			ER$^+$ breast cancer			ER$^-$ breast cancer		
h/wk Exercise	h/d Sitting	Cases	Person-years	IRR[a] (95% CI)	Cases	Person-years	IRR (95% CI)	Cases	Person-years	IRR (95% CI)
<1	<5	184	72,646	1.14 (0.78–1.66)	98	72,546	0.89 (0.57–1.42)	48	72,497	1.45 (0.65–3.22)
<1	5–9	352	139,461	1.24 (0.87–1.78)	180	139,268	0.93 (0.60–1.45)	104	139,200	1.73 (0.80–3.72)
<1	10+	200	83,625	1.22 (0.84–1.78)	86	83,495	0.79 (0.49–1.26)	66	83,477	1.89 (0.86–4.16)
1–4	<5	104	46,394	1.12 (0.75–1.65)	60	46,346	0.94 (0.58–1.52)	24	46,306	1.20 (0.51–2.78)
1–4	5–9	206	101,305	1.11 (0.77–1.61)	109	101,202	0.86 (0.55–1.35)	59	101,154	1.46 (0.66–3.19)
1–4	10+	96	50,555	1.10 (0.74–1.64)	41	50,496	0.69 (0.41–1.16)	34	50,489	1.80 (0.79–4.07)
5+	<5	33	16,824	1.00 (Ref.)	23	16,814	1.00 (Ref.)	7	16,792	1.00 (Ref.)
5+	5–9	60	34,856	0.96 (0.63–1.47)	27	34,816	0.63 (0.36–1.10)	24	34,812	1.76 (0.76–4.09)
5+	10+	29	20,177	0.85 (0.51–1.40)	14	20,159	0.62 (0.32–1.20)	9	20,154	1.18 (0.44–3.18)

[a]IRRs adjusted for age (single year), time period (questionnaire cycle), BMI (<25, 25–29, ≥30 kg/m^2), years of education (≤12, 13–15, 16, ≥17), parity (0, 1, 2, ≥3), vegetable/fruit dietary pattern (quintiles), and meat/fried foods dietary pattern (quintiles).

to determine the association in that subgroup. In the NIH-AARP follow-up study of postmenopausal women, there was also little association with ER^+ cancer (2,083 cases), whereas there was a significant inverse association with ER^- breast cancer (411cases; ref. 16). In contrast, other studies of premenopausal and postmenopausal women (7, 12, 15) and of postmenopausal women only (13, 17, 18) have found no difference by ER status. In the Women's Health Initiative study of postmenopausal women, physical activity at baseline was inversely associated but not significantly with risk of both ER^+ and triple-negative breast cancer (19). Our results on triple-negative cancer were close to the null, but confidence intervals were wide.

We found no statistically significant differences in the associations of baseline vigorous exercise with breast cancer risk in categories of age, BMI, parity, family history of breast cancer, and menopausal status, although an inverse association was stronger among women younger than 50 years of age than among older women. Associations in previous studies have varied across subgroups but not consistently (1–6).

There were small nonsignificant increases in risk of breast cancer associated with long hours of sitting at work or watching TV. An analysis of the 2 types of sitting jointly with vigorous exercise did not provide evidence for an increase in breast cancer risk in the women who were least active. In the American Cancer Society Cancer Prevention Study II (18) and the NIH-AARP Diet and Health Study (35), both of postmenopausal women, time sitting was associated with small nonsignificant increases in breast cancer incidence.

Exercise might lead to lower incidence of breast cancer through biologic mechanisms (3, 36, 37) that include reductions in menstrual cycles and ovarian hormones (4, 38–42), reductions in weight gain and obesity (4), reductions in hyperinsulinemia, insulin resistance, and insulin-like growth factor (IGF)I (43, 44), effects on cellular proliferation and apoptosis in mammary tissues (45), and effects on inflammation and immune function (46, 47). Our results do not support an influence of physical activity through effects on weight gain and obesity, because control for BMI did not change the IRRs, associations did not vary across categories of BMI, and associations were not stronger among postmenopausal women.

Data on physical activity were collected prospectively in the present study, thus obviating concern about reporting bias. Case–control studies have tended to find stronger associations of physical activity with breast cancer risk than follow-up studies. This difference could reflect better collection of detailed data on physical activity in the case–control studies. On the other hand, it could also reflect bias in the case–control studies from differential reporting of exercise by case–control status or disproportionate participation of more educated potential controls. The usefulness of the data reported on recent vigorous exercise in the present study is supported by 2 lines of evidence: in a BWHS validation study, self-report of recent vigorous exercise was significantly associated with an objective measure of physical activity (25), and vigorous exercise was associated with reduced incidence of type 2 diabetes (48) and obesity (49) in the BWHS, as expected. We had no validation data on exercise at the age of 30 years or 21 years or high school; exercise at these earlier time periods may have been reported less accurately than recent exercise. We also had no validation data on hours per day of sitting, but hours per day of sitting watching TV was associated with a significant increase in risk of diabetes in the BWHS, independent of recreational exercise (48). Participants will have varied in their definitions of vigorous exercise and of brisk walking, and random misclassification will have tended to reduce the associations of the more extreme categories of exercise with breast cancer risk. However, brisk walking as defined in the present study was associated with reduced incidence of type 2 diabetes in the BWHS (48). Lack of information on moderate-intensity activities other than walking is a limitation of the present study. Follow-up of the cohort for breast cancer was excellent, reducing concern about bias due to selective losses, and important potential confounding factors were controlled. ER status was determined by many institutions using their own parameters, and misclassification will have tended to reduce any differences between molecular subtypes.

In summary, the present study adds to the small body of evidence on exercise and breast cancer incidence in African-American women. The results suggest that high levels of recent vigorous exercise or brisk walking may result in a reduction in the incidence breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the NIH. Data on breast cancer pathology were obtained from several state cancer registries (AZ, CA, CO, CT, DE, DC, FL, GA, IL, IN, KY, LA, MD, MA, MI, NJ, NY, NC, OK, PA, SC, TN, TX, VA), and results reported do not necessarily represent their views.

Authors' Contributions

Conception and design: L. Rosenberg, J.R. Palmer, L.L. Adams-Campbell
Development of methodology: L. Rosenberg, J.R. Palmer, L.L. Adams-Campbell
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Rosenberg, J.R. Palmer
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Rosenberg, J.R. Palmer, Y. Ban, K. Kipping-Ruane, L.L. Adams-Campbell
Writing, review, and/or revision of the manuscript: L. Rosenberg, J.R. Palmer, T.N. Bethea, K. Kipping-Ruane, L.L. Adams-Campbell
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Rosenberg
Study supervision: L. Rosenberg, L.L. Adams-Campbell

Grant Support

This work was supported by the National Cancer Institute (R01 CA058420 and UM1 CA164974 to L. Rosenberg).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 23, 2014; revised July 22, 2014; accepted July 24, 2014; published OnlineFirst August 7, 2014.

References

1. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med 2008;42:636–47.
2. Gammon MD, John EM, Britton JA. Recreational and occupational physical activities and risk of breast cancer. J Natl Cancer Inst 1998;90:100–17.
3. Monninkhof EM, Elias SG, Vlems FA, van der Tweel I, Schuit AJ, Voskuil DW, et al. Physical activity and breast cancer: a systematic review. Epidemiology 2007;18:137–57.
4. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR; 2007.
5. World Cancer Research Fund/American Institute for Cancer Research. Continuous update: Project report summary. Food, nutrition, physical activity, and the prevention of breast cancer. Washington, DC: AICR; 2010.
6. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat 2013;137:869–82.
7. Bernstein L, Patel AV, Ursin G, Sullivan-Halley J, Press MF, Deapen D, et al. Lifetime recreational exercise activity and breast cancer risk among black women and white women. J Natl Cancer Inst 2005;97: 1671–9.
8. Cohen SS, Matthews CE, Bradshaw PT, Lipworth L, Buchowski MS, Signorello LB, et al. Sedentary behavior, physical activity, and likelihood of breast cancer among black and white women: a report from the southern community cohort study. Cancer Prev Res (Phila) 2013; 6:566–76.
9. John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in a multiethnic population: the San Francisco Bay area breast cancer study. Cancer Epidemiol Biomarkers Prev 2003;12: 1143–52.
10. Ratnasinghe LD, Modali RV, Seddon MB, Lehman TA. Physical activity and reduced breast cancer risk: a multinational study. Nutr Cancer 2010;62:425–35.
11. Sheppard VB, Makambi K, Taylor T, Wallington SF, Sween J, Adams-Campbell L. Physical activity reduces breast cancer risk in African American women. Ethn Dis 2011;21:406–11.
12. Adams SA, Matthews CE, Hebert JR, Moore CG, Cunningham JE, Shu XO, et al. Association of physical activity with hormone receptor status: the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev 2006;15:1170–8.
13. Bardia A, Hartmann LC, Vachon CM, Vierkant RA, Wang AH, Olson JE, et al. Recreational physical activity and risk of postmenopausal breast cancer based on hormone receptor status. Arch Intern Med 2006; 166:2478–83.
14. Dallal CM, Sullivan-Halley J, Ross RK, Wang Y, Deapen D, Horn-Ross PL, et al. Long-term recreational physical activity and risk of invasive and *in situ* breast cancer: the California teachers study. Arch Intern Med 2007;167:408–15.
15. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from two case-control studies. Cancer Epidemiol Biomarkers Prev 2000;9:681–7.
16. Peters TM, Schatzkin A, Gierach GL, Moore SC, Lacey JV Jr, Wareham NJ, et al. Physical activity and postmenopausal breast cancer risk in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev 2009;18:289–96.
17. Leitzmann MF, Moore SC, Peters TM, Lacey JV Jr, Schatzkin A, Schairer C, et al. Prospective study of physical activity and risk of postmenopausal breast cancer. Breast Cancer Res 2008;10:R92.
18. Hildebrand JS, Gapstur SM, Campbell PT, Gaudet MM, Patel AV. Recreational physical activity and leisure-time sitting in relation to postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 2013;22:1906–12.
19. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Stefanick ML, Wactawski-Wende J, et al. Body size, physical activity, and risk of triple-negative and estrogen receptor-positive breast cancer. Cancer Epidemiol Biomarkers Prev 2011;20:454–63.
20. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst 2005;97:439–48.
21. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. Cancer 2007;109:1721–8.
22. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. Jama 2006;295:2492–502.
23. Adams-Campbell LL, Rosenberg L, Rao RS, Palmer JR. Strenuous physical activity and breast cancer risk in African-American women. J Natl Med Assoc 2001;93:267–75.
24. Russell CW, Boggs DA, Palmer JR, Rosenberg L. Use of a web-based questionnaire in the Black Women's Health Study. Am J Epidemiol 2010;172:1286–91.
25. Carter-Nolan PL, Adams-Campbell LL, Makambi K, Lewis S, Palmer JR, Rosenberg L. Validation of physical activity instruments: Black Women's Health Study. Ethn Dis 2006;16:943–7.
26. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1:58–64.
27. Boggs DA, Palmer JR, Spiegelman D, Stampfer MJ, Adams-Campbell LL, Rosenberg L. Dietary patterns and 14-y weight gain in African American women. Am J Clin Nutr 2011;94:86–94.
28. Furberg H, Millikan R, Dressler L, Newman B, Geradts J. Tumor characteristics in African American and white women. Breast Cancer Res Treat 2001;68:33–43.
29. Gapstur SM, Dupuis J, Gann P, Collila S, Winchester DP. Hormone receptor status of breast tumors in black, Hispanic, and non-Hispanic white women. An analysis of 13,239 cases. Cancer 1996;77:1465–71.
30. Parise CA, Bauer KR, Caggiano V. Variation in breast cancer subtypes with age and race/ethnicity. Crit Rev Oncol Hematol 2009;76:44–52.
31. Palmer JR, Boggs DA, Wise LA, Ambrosone CB, Adams-Campbell LL, Rosenberg L. Parity and lactation in relation to estrogen receptor negative breast cancer in African American women. Cancer Epidemiol Biomarkers Prev 2011;20:1883–91.
32. Rosenberg L, Boggs DA, Wise LA, Adams-Campbell LL, Palmer JR. Oral contraceptive use and estrogen/progesterone receptor-negative breast cancer among African American women. Cancer Epidemiol Biomarkers Prev 2010;19:2073–9.
33. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25: 71–80.
34. Therneau T. Extending the Cox model. In:Lin DY, Fleming TR, editors. Proceedings of the first Seattle symposium in biostatistics: survival analysis. New York: Springer Verlag; 1997. p. 51–84.
35. George SM, Irwin ML, Matthews CE, Mayne ST, Gail MH, Moore SC, et al. Beyond recreational physical activity: examining occupational and household activity, transportation activity, and sedentary behavior in relation to postmenopausal breast cancer risk. Am J Public Health 2010;100:2288–95.
36. Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. Cancer Epidemiol Biomarkers Prev 2009;18:11–27.
37. Friedenreich CM. Physical activity and breast cancer: review of the epidemiologic evidence and biologic mechanisms. Recent Results Cancer Res 2011;188:125–39.
38. Bonen A, Ling WY, MacIntyre KP, Neil R, McGrail JC, Belcastro AN. Effects of exercise on the serum concentrations of FSH, LH, progesterone, and estradiol. Eur J Appl Physiol Occup Physiol 1979;42:15–23.
39. Jurkowski JE, Jones NL, Walker C, Younglai EV, Sutton JR. Ovarian hormonal responses to exercise. J Appl Physiol 1978;44:109–14.
40. Tymchuk CN, Tessler SB, Barnard RJ. Changes in sex hormone-binding globulin, insulin, and serum lipids in postmenopausal women on a low-fat, high-fiber diet combined with exercise. Nutr Cancer 2000;38:158–62.

Published OnlineFirst August 7, 2014; DOI: 10.1158/1055-9965.EPI-14-0448

41. Nestler JE. Obesity, insulin, sex steroids and ovulation. Int J Obes Relat Metab Disord 2000;24 Suppl 2:S71–3.
42. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. Am J Epidemiol 2000;151:703–14.
43. Mayer-Davis EJ, Vitolins MZ, Carmichael SL, Hemphill S, Tsaroucha G, Rushing J, et al. Validity and reproducibility of a food frequency interview in a multi-cultural epidemiology study. Ann Epidemiol 1999;9:314–24.
44. Fletcher O, Gibson L, Johnson N, Altmann DR, Holly JM, Ashworth A, et al. Polymorphisms and circulating levels in the insulin-like growth factor system and risk of breast cancer: a systematic review. Cancer Epidemiol Biomarkers Prev 2005;14:2–19.
45. Westerlind KC, McCarty HL, Gibson KJ, Strange R. Effect of exercise on the rat mammary gland: implications for carcinogenesis. Acta Physiol Scand 2002;175:147–56.
46. Rundle A. Molecular epidemiology of physical activity and cancer. Cancer Epidemiol Biomarkers Prev 2005;14:227–36.
47. Shephard RJ, Shek PN. Associations between physical activity and susceptibility to cancer: possible mechanisms. Sports Med 1998;26:293–315.
48. Krishnan S, Rosenberg L, Palmer JR. Physical activity and television watching in relation to risk of type 2 diabetes: the Black Women's Health Study. Am J Epidemiol 2009;169:428–34.
49. Rosenberg L, Kipping-Ruane KL, Boggs DA, Palmer JR. Physical activity and the incidence of obesity in young African-American women. Am J Prev Med 2013;45:262–8.

Published OnlineFirst August 7, 2014; DOI: 10.1158/1055-9965.EPI-14-0448

Cancer Epidemiology, Biomarkers & Prevention

American Association for Cancer Research

A Prospective Study of Physical Activity and Breast Cancer Incidence in African-American Women

Lynn Rosenberg, Julie R. Palmer, Traci N. Bethea, et al.

Cancer Epidemiol Biomarkers Prev 2014;23:2522-2531. Published OnlineFirst August 7, 2014.