Recreational Physical Activity and the Risk of Breast Cancer in Postmenopausal Women

The Women's Health Initiative Cohort Study

Anne McTiernan, MD, PhD
Charles Kooperberg, PhD
Emily White, PhD
Sara Wilcox, PhD
Ralph Coates, PhD
Lucile L. Adams-Campbell, PhD
Nancy Woods, PhD
Judith Ockene, PhD

Context Women who are physically active have a decreased risk for breast cancer, but the types, amounts, and timing of activity needed are unknown.

Objective To prospectively examine the association between current and past recreational physical activity and incidence of breast cancer in postmenopausal women.

Design, Setting, and Patients Prospective cohort study in 74 171 women aged 50 to 79 years who were recruited by 40 US clinical centers from 1993 through 1998.

Main Outcome Measure Incident invasive and in situ breast cancer.

Results We documented 1780 newly diagnosed cases of breast cancer over a mean follow-up of 4.7 years. Compared with less active women, women who engaged in regular strenuous physical activity at age 35 years had a 14% decreased risk of breast cancer (relative risk [RR], 0.86; 95% confidence interval [CI], 0.78-0.95). Similar but attenuated findings were observed for strenuous physical activity at ages 18 years and 50 years. An increasing total current physical activity score was associated with a reduced risk for breast cancer ($P=.03$ for trend). Women who engaged in the equivalent of 1.25 to 2.5 hours per week of brisk walking had an 18% decreased risk of breast cancer (RR, 0.82; 95% CI, 0.68-0.97) compared with inactive women. Slightly greater reduction in risk was observed for women who engaged in the equivalent of 10 hours or more per week of brisk walking. The effect of exercise was most pronounced in women in the lowest tertile of body mass index (BMI) (<24.1), but also was observed for women in the middle tertile of BMI (24.1-28.4).

Conclusions These data suggest that increased physical activity is associated with reduced risk for breast cancer in postmenopausal women, longer duration provides most benefit, and that such activity need not be strenuous.

JAMA. 2003;290:1331-1336 www.jama.com

WOMEN WHO ENGAGE IN regular exercise have been shown to have a reduced risk of breast cancer.[1-4] It is not clear if physical activity after menopause reduces the risk of breast cancer or if life-long physical activity is required. The intensity and amount of exercise needed to reduce risk are unknown, and some studies have suggested that strenuous activity is needed for risk reduction.[1,5] It is important to determine if moderate physical activity late in life can reduce risk of breast cancer, since this can be achieved by most women.

We therefore examined the association between recreational physical activity in adulthood and breast cancer incidence in a large, ethnically and racially diverse cohort of older women from the Women's Health Initiative (WHI) Observational Study. Using detailed assessments of physical activity, we assessed the associations between physical activity (past strenuous activity at ages 18, 35, and 50 years, and current total physical activity score, hours per week of strenuous activity, and combined hours per week of moderate and strenuous activity) and incidence of breast cancer.

See also pp 1323 and 1377.

METHODS

Study Population

The study population consisted of 74 171 women who were enrolled in the WHI Observational Study, a multicenter, multiethnic cohort of postmenopausal

Author Affiliation: Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Wash (Drs McTiernan, Kooperberg, and White); Department of Exercise Science, Norman J. Arnold School of Public Health, University of South Carolina, Columbia (Dr Wilcox); Division of Cancer Prevention and Control, NCCDPHP, Centers for Disease Control and Prevention, Atlanta, Ga (Dr Coates); Howard University Cancer Center, Washington, DC (Dr Adams-Campbell); School of Nursing, University of Washington, Seattle (Dr Woods); Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester (Dr Ockene).
Corresponding Author and Reprints: Anne McTiernan, MD, PhD, Fred Hutchinson Cancer Research Center, PO Box 98109-1024, MP-900, Seattle, WA 98109 (e-mail: amctiern@fhcrc.org).

women aged 50 to 79 years at study entry.[6] A total of 93 676 women were enrolled into the study between October 1993 and December 1998 from 40 US clinical centers. Women were eligible for the study if they were aged 50 to 79 years, postmenopausal, planned to live in the clinical center area for at least 3 years, and free of serious health conditions that might reduce survival during the 3 years (eg, class IV congestive heart failure, obstructive lung disease requiring supplemental oxygen, or severe chronic liver or kidney disease). Women were excluded from the present analysis if they reported a history of breast cancer on study entry or had missing physical activity or covariate data. The women included in these analyses represented a diverse cohort of US women including 10 863 (15%) African American, Hispanic (Mexican American, Puerto-Rican Hispanic, and Cuban Hispanic), Asian/Pacific Islander (Japanese, Chinese, Hawaiian), and Native American women.[7] Details of the scientific rationale, design, eligibility requirements, and baseline characteristics of the cohort have been published previously.[6,7]

All participants signed informed consent forms. The institutional review boards at all participating institutions, including the coordinating center, subcontractors, and clinical centers, approved the study protocols and procedures.

The follow-up rates for medical history updates in years 1, 2, 4, 5, and 6 (the years in which medical histories were collected by mail) were 96%, 94%, 94%, 95%, and 94%, respectively. As of February 28, 2002, 3.2% of the women stopped participation or have been lost to follow-up, and 2.7% have died.

Exposure Assessment

All exposure information in this analysis was collected when women entered the study. A standardized written protocol, centralized training of clinic staff, and periodic quality assurance visits by the coordinating center were used to ensure uniform administration of data collection instruments.

At a required baseline screening clinic visit, participants completed several self-administered questionnaires, including medical history, reproductive and menstrual history, health behavior including physical activity and diet, and family history of select diseases including breast cancer. Staff collected anthropometric measures (height, weight, waist circumference) and interviewed participants regarding lifetime use of hormone therapy.

Women first were asked (yes/no) if they usually did strenuous or very hard exercises (long enough to work up a sweat and make their heart beat fast) at least 3 times per week at ages 18, 35, and 50 years. Participants then were asked how often they currently (at study entry) walked outside the home for more than 10 minutes without stopping, the usual duration, and the speed. Categories of frequency were rarely/never, 1 to 3 times per month, 1 time per week, 2 to 3 times per week, 4 to 6 times per week, and 7 or more times per week. Duration categories were less than 20 minutes, 20 to 39 minutes, 40 to 59 minutes, and 1 hour or more. Four speed categories ranged from less than 2 mph (casual walking) to more than 4 mph (very fast).

Women then were asked how often they currently (at study entry) exercised at strenuous levels (that increased heart rate and produced sweating) by checking categories never, 1, 2, 3, 4, or 5 d/wk or more, and for how long they exercised at each session by checking categories less than 20 minutes, 20 to 39 minutes, 40 to 59 minutes, or 1 hour or more. Examples provided of strenuous activities included aerobics, aerobic dancing, jogging, tennis, and swimming laps. Women were asked similar questions about moderate- and low-intensity physical activities. Examples provided of moderate-intensity activities included biking outdoors, using an exercise machine, calisthenics, easy swimming, and popular or folk dancing; and examples provided of low-intensity activities included slow dancing, bowling, and golf.

We constructed several composite current physical activity variables. We imputed the midpoint value for ranges of frequency and duration of exercise sessions. We multiplied minutes × frequency to create a variable "hours exercised per week," separately for strenuous, moderate, light, and 3 intensities of walking. We assigned metabolic equivalent (MET) values for strenuous-, moderate-, and low-intensity activities as 7, 4, and 3 METs, respectively.[8] For mean speed of walking (average [2-3 mph], fast [3-4 mph], and very fast [>4 mph]), we assigned MET values of 3, 4, and 4.5, respectively. We computed a current total physical activity variable (MET-hours/week) by multiplying the MET level for the activity by the hours exercised per week and summing values for all of the types of activities.

Age at menopause was determined as the youngest age when the participant experienced any of the following: last menstrual bleeding (all participants were ≥12 months after last menstrual period), removal of both ovaries, or beginning of hormone therapy. Age at first birth was calculated as the age at first pregnancy of 6 months' duration or longer. Total daily kilocalorie intake and percentage of kilocalories from fat were assessed with a 120-item semiquantitative food frequency questionnaire developed and tested for the WHI.[9]

Reproducibility and Validation of the Physical Activity Assessment

Among a random sample of 536 participants, second measures of all physical activity variables were ascertained approximately 10 weeks after baseline. The test-retest reliability (weighted κ) for the physical activity variables ranged from 0.53 to 0.72, and the intraclass correlation for the total physical activity variable was 0.77.[7]

Ascertainment of End Points

Study physicians and cancer coders, blinded to exposure status, reviewed pathology reports, discharge summaries, operative reports, and radiology reports for all biopsies and surgeries and coded cases according to National Can-

cer Institute Surveillance, Epidemiology, and End Results guidelines.[10,11]

Statistical Analyses

The physical activity questions on past and current activity collected at study baseline were used in the analyses. Follow-up time for each woman was accrued from enrollment to the date of diagnosis of breast cancer, death from a non–breast cancer cause, loss to follow-up, or administrative censor date (April 30, 2002). Age-adjusted relative risks (RRs) were computed as the incidence rate in a specific category of activity divided by the incidence rate in the "no activity" category.

For analyses of past activities, we used "strenuous activity at age 18," "strenuous activity at age 35," and "strenuous activity at age 50," as binary covariates. For total current physical activity, we created indicator variables for no activity, 5 MET-h/wk or less, 5.1 to 10 MET-h/wk, 10.1 to 20 MET-h/wk, 20.1 to 40 MET-h/wk, and more than 40 MET-h/wk. For combined moderate/strenuous exercise we created indicator variables for no activity, 1 h/wk or less, 1.1 to 2 h/wk, 2.1 to 3 h/wk, 3.1 to 4 h/wk, 4.1 to 7 h/wk, and more than 7 h/wk. For hours of strenuous exercise, the indicator variables were for no activity, 1 h/wk or less, 1.1 to 2 h/wk, 2.1 to 4 hours h/wk, and more than 4 h/wk.

We used stratified adjustment and Cox proportional hazards regression model[12] to adjust simultaneously for potential confounding variables. Categorical variables included age, body mass index ([BMI] calculated as weight in kilograms divided by the square of height in meters), use of hormone therapy, race, geographic region, income, education, ever breastfed, hysterectomy status, first-degree relative with breast cancer, smoking status, parity, age at first birth, number of mammograms in 5 years before study enrollment, and use of alcohol. Continuous variables included age at menarche and age at menopause. In a separate analysis, we also adjusted for daily kilocalorie intake and percentage of calories from fat as continuous variables.

Table 1. Risk of Breast Cancer According to Past Participation (No/Yes) in Strenuous Physical Activity at Ages 18, 35, and 50 Years

	No. of Cases	No. of Noncases	Annualized Incidence Rate Per 100	Relative Risk* (95% Confidence Intervals)	*P* Value
Age 18 y					
No	984	38 514	0.53	1.00	.21
Yes	725	30 837	0.49	0.94 (0.85-1.04)	
Age 35 y					
No	1032	38 475	0.56	1.00	.003
Yes	687	31 107	0.46	0.86 (0.78-0.95)	
Age 50 y					
No	1074	42 204	0.53	1.00	.08
Yes	673	27 922	0.50	0.92 (0.83-1.01)	

*Adjusted for 5-year age groups, body mass index (tertiles), hormone therapy status (current/past/never), race, geographic region, income, education, ever breastfed, hysterectomy status, first-degree relative with breast cancer, smoking status, parity, age at first birth, number of mammograms in 5 years before study enrollment, and alcohol use as categorical variables, and age at menarche and age at menopause as continuous variables.

To assess the relative contributions of strenuous and moderate activity to the total physical activity effect on breast cancer risk, we tested 2 additional models of total physical activity effect on breast cancer risk including as adjustment variables percentage of total activities that were strenuous intensity and percentage of total activities that were moderate or strenuous intensity. We also assessed the association between these 2 variables and breast cancer risk in separate models. Analyses were performed using S-Plus (Insightful Inc, Seattle, Wash).

RESULTS

During a mean length of follow-up of 4.7 years (347 519 woman-years of observation), we identified 1780 newly diagnosed cases of breast cancer. Of these, 1537 cases had central coding complete: 85% were invasive (75.5% stage I, 3.6% stage II), and 85% were estrogen receptor positive.

Women who engaged in strenuous physical activity at least 3 times per week at age 35 years had a statistically significant decreased risk of breast cancer of 14% (RR, 0.86; 95% CI, 0.78-0.95) compared with women who did not engage in this level of activity (TABLE 1). Results for invasive and in situ cancers were similar, although the results were statistically significant only for invasive cancers ($P=.006$, data not shown). Similarly, women who reported engaging in strenuous physical activity at least 3 times per week at age 50 years had a slight, nonstatistically significant reduction in risk of overall breast cancer. There was a statistically significant reduction in risk of invasive cancer of 11% ($P=.04$) and no difference in risk of in situ cancer compared with women who did not engage in regular strenuous activity at this age (data not shown). Regular strenuous activity at age 18 years was associated with only a marginally decreased risk of breast cancer.

Increased amount of total current physical activity (increased MET-hours per week) was associated with a reduced risk of breast cancer ($P=.03$ for trend) (TABLE 2). Women who exercised on average for 5.1 to 10.0 MET-h/wk (approximately equal to 1.25-2.5 h/wk of brisk walking or equivalent exercise, or more hours of lower-intensity exercise) had a statistically significant reduction in risk of developing breast cancer of 18% compared with sedentary women (RR, 0.82; 95% CI, 0.68-0.97). Women who exercised more than 40 MET-h/wk had a 22% reduction in risk compared with sedentary women (RR, 0.78; 95% CI, 0.62-1.0). Women who engaged in more than 7 h/wk of moderate/strenuous physical activity had a 21% reduced risk of breast cancer compared with sedentary women (RR, 0.79; 95% CI, 0.63-0.99). Increased strenuous physical activity was associated with a slightly reduced risk for breast cancer that was not statistically significant ($P=.25$ for trend).

Adjustment of total activity for either percentage of total activities that

were strenuous intensity or percentage of activities that were moderate or strenuous intensity did not change the results (data not shown). In that model, neither percentage of total activities that were strenuous intensity nor percentage of activities that were moderate or strenuous intensity were associated with risk of breast cancer (data not shown).

We examined risk of breast cancer associated with physical activity in tertiles of BMI (TABLE 3). Among women in the lowest tertile of BMI (≤24.13), a strong and significant reduction in risk of breast cancer with increasing level of total current physical activity was observed ($P=.03$ for trend). Women in this BMI group who engaged in 5.1 to 10 MET-h/wk of physical activity had a 30% reduction in risk for breast cancer (RR, 0.70; 95% CI, 0.51-0.97). Women who engaged in 20.1 to 40.0 MET-h/wk (approximately 5-10 h/wk of brisk walking) had a 32% reduction in breast cancer risk (RR, 0.68; 95% CI, 0.51-0.92). More than 40 MET-h/wk decreased risk even further (RR, 0.63;

Table 2. Risk of Breast Cancer According to Amount of Current (Study Entry) Strenuous, Moderate/Strenuous, and Total Physical Activity (MET-h/wk)

	Total Current Physical Activity, MET-h/wk						
	None	≤5	5.1-10	10.1-20	20.1-40	>40	*P* Value for Trend
No. of cases	239	351	270	456	355	97	
No. of noncases	9391	14 435	11 717	17 483	14 299	4277	
Annualized incidence rate per 100	0.54	0.51	0.48	0.54	0.51	0.47	
RR (95% CI)*	1.00	0.90 (0.77-1.07)	0.82 (0.68-0.97)	0.89 (0.76-1.00)	0.83 (0.70-0.98)	0.78 (0.62-1.00)	.03
	Current Moderate or Strenuous Physical Activity, h/wk						
	None	≤1	1.1-2	2.1-3	3.1-4	4.1-7	>7
No. of cases	617	202	260	211	171	222	85
No. of noncases	25 124	8632	10 674	8077	6242	8797	4056
Annualized incidence rate per 100	0.52	0.49	0.51	0.54	0.56	0.52	0.43
RR (95% CI)*	1.00	0.92 (0.78-1.10)	0.91 (0.79-1.10)	0.94 (0.81-1.10)	0.99 (0.83-1.20)	0.91 (0.78-1.10)	0.79 (0.63-0.99)	.12
	Current Strenuous Physical Activity, h/wk						
	None	≤1	1.1-2	2.1-4	>4		
No. of cases	1281	157	137	149	44		
No. of noncases	51 726	6562	5430	6018	1866		
Annualized incidence rate per 100	0.52	0.49	0.52	0.51	0.49		
RR (95% CI)*	1.00	0.94 (0.80-1.10)	0.95 (0.80-1.10)	0.93 (0.78-1.10)	0.91 (0.67-1.20)		.25

Abbreviation: MET, metabolic equivalent.
*Adjusted for 5-year age groups, body mass index (tertiles), hormone therapy status (current/past/never), race, geographic region, income, education, ever breastfed, hysterectomy status, first-degree relative with breast cancer, smoking status, parity, age at first birth, number of mammograms in 5 years before study enrollment, and alcohol use as categorical variables, and age at menarche and age at menopause as continuous variables.

Table 3. Risk of Breast Cancer According to Amount of Current (Study Entry) Total Physical Activity (MET-h/wk) by Tertiles of Body Mass Index (BMI)

	BMI											
	≤24.13				24.14-28.44				>28.44			
	No. of Cases	No. of Noncases	Annualized Incidence Rate per 100	RR* (95% CI)	No. of Cases	No. of Noncases	Annualized Incidence Rate per 100	RR* (95% CI)	No. of Cases	No. of Noncases	Annualized Incidence Rate per 100	RR* (95% CI)
All activities, MET-h/wk												
None	63	2116	0.62	1.00	72	2695	0.57	1.00	104	4580	0.49	1.00
0-5.0	94	3809	0.52	0.78 (0.57-1.1)	95	4645	0.43	0.72 (0.53-0.98)	162	5981	0.57	1.1 (0.88-1.5)
5.1-10.0	86	3742	0.47	0.70 (0.51-0.97)	96	4042	0.49	0.78 (0.57-1.1)	88	3933	0.47	0.90 (0.67-1.2)
10.1-20.0	179	6492	0.56	0.80 (0.6-1.1)	149	6200	0.50	0.77 (0.58-1.0)	128	4791	0.57	1.0 (0.79-1.3)
20.1-40	149	6173	0.49	0.68 (0.51-0.92)	133	5005	0.55	0.85 (0.64-1.1)	73	3121	0.49	0.89 (0.65-1.2)
≥40	44	2080	0.43	0.63 (0.43-0.93)	35	1467	0.50	0.78 (0.52-1.2)	18	730	0.52	0.94 (0.57-1.6)
P for trend				.03				.74				.30

Abbreviations: CI, confidence interval; MET, metabolic equivalent; RR, relative risk.
*Adjusted for 5-year age groups, hormone therapy status (current/past/never), race, geographic region, income, education, ever breastfed, hysterectomy status, first-degree relative with breast cancer, smoking status, parity, age at first birth, number of mammograms in 5 years before study enrollment, and alcohol use as categorical variables, and age at menarche and age at menopause as continuous variables.

95% CI, 0.43-0.93). Among women in the middle tertile of BMI, increased total physical activity was associated with a reduced risk of breast cancer, but the associations were only statistically significant for 5 MET-h/wk or less (RR compared with no activity, 0.72; 95% CI, 0.53-0.98). Increased total current physical activity was not associated with a reduced risk of breast cancer among women in the heaviest tertile of BMI.

Adjustment for either daily kilocalorie intake or percentage of calories from fat did not change any of these results (data not shown).

We also examined the effects of physical activity on risk of breast cancer among tertiles of waist circumference (data not shown). Overall, increased MET-hours per week of total physical activity was associated with decreased risk of breast cancer across all categories of waist circumference, although the effect was strongest for the women in the lowest 2 tertiles of waist circumference. None of the tests for trend was statistically significant.

We examined the effect of physical activity on risk of breast cancer among several other subgroups including age (50-59, 60-69, 70-79 years), parity (parous/nulliparous), family history of breast cancer (any/none), and use of hormone therapy (current/past/never). The reduced risk associated with increased levels of total physical activity was seen across all categories of these variables. Results for risk of estrogen-receptor positive tumors were similar to the results for cases overall (data not shown).

COMMENT

These data from a large prospective cohort of postmenopausal US women support a protective role of physical activity against breast cancer, particularly past regular strenuous physical activity at ages 35 and 50 years, and current increased total physical activity. The greatest associations were observed for the lightest-weight women, although moderately overweight women also had benefit from increased total physical activity.

Strengths of the present study include the prospective design, the large size, the racial and ethnic diversity of the cohort, the detailed assessment of physical activity, and the uniform and strict criteria for the breast cancer end points. Other strengths of the study include the high rate of follow-up and the detailed information about potential confounding variables.

Although the WHI is a multiethnic, multiracial cohort, too few numbers of cases to report race- or ethnic-specific associations between physical activity and breast cancer risk were available. We looked at the data for whites alone and for African Americans alone, the 2 largest racial/ethnic subgroups of cases, and found that the associations were similar to the overall analyses (data not shown). We did not collect detailed data on lifetime physical activity. However, we did collect information about strenuous exercise at ages 18, 35, and 50 years and found that regular strenuous exercise at the latter 2 age points was protective against breast cancer. Some of the physical activity questions grouped exercises together into those that are most often low, moderate, or vigorous in intensity. If individual women performed activities at other intensities, there would be misclassification of intensity. The use of imputed midpoint values for ranges of physical activity data could have introduced error. Only data on recreational and walking activities were collected. The resulting nondifferential misclassification of exposure to physical activity would be expected to bias the risk estimate toward unity, thus the observed association between increased physical activity and reduced risk for breast cancer is likely real. Finally, the study population, although representing more diverse racial, ethnic, and social backgrounds than most previously studied cohorts, is not an entirely representative cross-section of US women.

Several published cohort studies[13-25] have investigated the association between physical activity and risk of breast cancer in postmenopausal women, of which all but a few[23,24] found a reduced risk for breast cancer in women who were classified at the highest levels of physical activity. The reduction in risk ranged from 10% to 70% for the most active women. The definition of "most active" varied by study.

A few other cohort and case-control studies have found that risk reduction associated with physical activity was limited to the leanest or middleweight compared with obese postmenopausal women.[17,20,26,27] These results were similar to our findings, although others have found no effect of adiposity on the association betweeen physical activity and breast cancer.[5,18,24,28]

Several mechanisms have been proposed to explain the association between increased physical activity and reduced risk for breast cancer. For exercise in the postmenopausal years, the most likely mechanism is reduction in body fat leading to reduced substrate for production of estrogen from androgen in fat tissue through aromatization.[2,29] Physical activity also could increase levels of sex hormone binding globulin,[30] thereby reducing the amount of estradiol in the free, most biologically active, state. Another potential mechanism is through exercise reduction of insulin and other growth factors.[2,31] Another analysis of these data showed that increased adiposity was associated with increased risk for breast cancer, although the effect was limited to women who had never used hormone therapy.[32]

The results of this study suggest that physical inactivity may be a modifiable risk factor for which postmenopausal women can make changes to reduce their risk of breast cancer. The finding that increased total recreational and walking physical activity reduces this risk is promising, although it may not be necessary for women to engage in strenuous activity in their older years to enjoy the protective effects of exercise. Another promising aspect of the study is that physical activity reduces risk among women who are using hormone therapy, a group that is at increased risk for developing breast cancer.[33] For those women who choose to continue taking hormone therapy for control of menopausal symptoms or for prevention of

osteoporosis, it will be welcome information that a simple modification of lifestyle to increase physical activity can reduce their risk of breast cancer.

Author Contributions: *Study concept and design:* McTiernan, Kooperberg, White, Adams-Campbell, Woods.
Acquisition of data: McTiernan, Kooperberg, Coates, Ockene.
Analysis and interpretation of data: McTiernan, Kooperberg, White, Wilcox, Coates.
Drafting of the manuscript: McTiernan.
Critical revision of the manuscript for important intellectual content: McTiernan, Kooperberg, White, Wilcox, Coates, Adams-Campbell, Woods, Ockene.
Statistical expertise: Kooperberg, White.
Obtained funding: Ockene.
Administrative, technical, or material support: McTiernan, Kooperberg, Ockene.
Study supervision: McTiernan.
List of Participating WHI Investigators:
Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Md) Jacques E. Rossouw, Linda Pottern, Shari Ludlam, Joan McGowan, Nancy Morris.
Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, Wash) Ross Prentice, Garnet Anderson, Andrea LaCroix, Ruth Patterson, Anne McTiernan; (Bowman Gray School of Medicine, Winston-Salem, NC) Sally Shumaker, Pentti Rautaharju; (Medical Research Labs, Highland Heights, Ky) Evan Stein; (University of California at San Francisco, San Francisco) Steven Cummings; (University of Minnesota, Minneapolis) John Himes; (University of Washington, Seattle) Susan Heckbert.
Clinical Centers: (Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, Tex) Jennifer Hays; (Brigham and Women's Hospital, Harvard Medical School, Boston, Mass) JoAnn Manson; (Brown University, Providence, RI) Annlouise R. Assaf; (Emory University, Atlanta, Ga) Lawrence Phillips; (Fred Hutchinson Cancer Research Center, Seattle, Wash) Shirley Beresford; (George Washington University Medical Center, Washington, DC) Judith Hsia; (Harbor-UCLA Research and Education Institute, Torrance, Calif) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, Ore) Cheryl Ritenbaugh; (Kaiser Permanente Division of Research, Oakland, Calif) Bette Caan; (Medical College of Wisconsin, Milwaukee) Jane Morley Kotchen; (Medstar Research Institute, Washington, DC) Barbara V. Howard; (Northwestern University, Chicago/Evanston, Ill) Linda Van Horn; (Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill) Henry Black; (Stanford Center for Research in Disease Prevention, Stanford University, Stanford, Calif) Marcia L. Stefanick; (State University of New York at Stony Brook, Stony Brook) Dorothy Lane; (The Ohio State University, Columbus) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham) Cora Beth Lewis; (University of Arizona, Tucson/Phoenix) Tamsen Bassford; (University at Buffalo, Buffalo, NY) Maurizio Trevisan; (University of California at Davis, Sacramento) John Robbins; (University of California at Irvine, Orange) Allan Hubbell; (University of California at Los Angeles) Howard Judd; (University of California at San Diego, La Jolla/Chula Vista) Robert D. Langer; (University of Cincinnati, Cincinnati, Ohio) Margery Gass; (University of Florida, Gainesville/Jacksonville) Marian Limacher; (University of Hawaii, Honolulu) David Curb; (University of Iowa, Iowa City/Davenport) Robert Wallace; (University of Massachusetts, Worcester) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark) Norman Lasser; (University of Miami, Miami, Fla) Mary Jo O'Sullivan; (University of Minnesota, Minneapolis) Karen Margolis; (University of Nevada, Reno) Robert Brunner; (University of North Carolina, Chapel Hill) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, Pa) Lewis Kuller; (University of Tennessee, Memphis) Karen C. Johnson; (University of Texas Health Science Center, San Antonio) Robert Schenken; (University of Wisconsin, Madison) Catherine Allen; (Wake Forest University School of Medicine, Winston-Salem, NC) Gregory Burke; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, Mich) Susan Hendrix.
Funding/Support: The research on which this publication is based was performed pursuant to contracts N01-WH-2-2110, N01-WH-4-2116, NO1-WH-4-2123, NO1-WH-3-2111, and NO1-WH-3-2100, with the National Institutes of Health, Department of Health and Human Services.

REFERENCES

1. Friedenreich CM. Physical activity and cancer prevention: from observational to intervention research. *Cancer Epidemiol Biomarkers Prev*. 2001;10:287-301.
2. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. *Cancer Causes Control*. 1998;9:487-509.
3. Vaino H, Bianchini F, and the International Agency for Research on Cancer Working Group on the Evaluation of Cancer-Preventive Agents, eds. *Weight Control and Physical Activity*. Lyon, France: International Agency for Research on Cancer; 2002. *IARC Handbooks of Cancer Prevention*; vol 6.
4. Byers T, Nestle M, McTiernan A, et al, and the American Cancer Society 2001 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with health food choices and physical activity. *CA Cancer J Clin*. 2002;52:92-119.
5. McTiernan A, Stanford JL, Weiss NS, Daling JR, Voigt LF. Occurrence of breast cancer in relation to recreational exercise in women age 50-64 years. *Epidemiology*. 1996;7:598-604.
6. Design of the Women's Health Initiative clinical trial and observational study: the Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19:61-109.
7. Langer RD, White E, Lewis CE, et al. Baseline characteristics of the participants in the Observational Study of the Women's Health Initiative and reliability of baseline measures. *Ann Epidemiol*. In press.
8. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25:71-80.
9. Patterson RE, Kristal AR, Tinker LF, Carter RA, Bolton MP, Agurs-Collins T. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9:178-87.
10. *SEER Program: Comparative Staging Guide for Cancer*. Washington, DC: US Dept of Health and Human Services, Public Health Service, National Institutes of Health; version 1.1, June 1993. NIH Publication 93-3640.
11. *The SEER Program Code Manual*. Cancer Statistics Branch, Surveillance Program, Division of Cancer Prevention and Control, National Cancer Institute, US Dept of Health and Human Services, Public Health Service, National Institutes of Health; June 1992. NIH Publication No. 92-1999.
12. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc Ser B Stat Soc*. 1972;34:187-220.
13. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. *N Engl J Med*. 1997; 336:1269-1275.
14. Fraser G. E., Shavlik D. Risk factors, lifetime risk, and age at onset of breast cancer. *Ann Epidemiol*. 1997;7:375-382.
15. Pukkala E, Poskiparta M, Apter D, Vihko V. Lifelong physical activity and cancer risk among Finnish female teachers. *Eur J Cancer Prev*. 1993;2:369-376.
16. Luoto R, Latikka P, Pukkala E, Hakulinin T, Vihko V. The effect of physical activity on breast cancer risk: a cohort study of 30,548 women. *Eur J Epidemiol*. 2000;16:973-980.
17. Dirx MJM, Voorrips LE, Goldbohm RA, van den Brandt PA. Baseline recreational physical activity, history of sports participation, and postmenopausal breast carcinoma risk in the Netherlands Cohort Study. *Cancer*. 2001;92:1638-1649.
18. Breslow RA, Ballard-Barbash R, Munoz K, Graubard BI. Long-term recreational physical activity and breast cancer in the National Health and Nutrition Examination Survey, I: epidemiologic follow-up study. *Cancer Epidemiol Biomarkers Prev*. 2001;10:805-808.
19. Lee IM, Rexrode KM, Cook NR, Hennekens CH, Buring JE. Physical activity and breast cancer risk: the Women's Health Study (United States). *Cancer Causes Control*. 2001;12:137-145.
20. Moradi T, Adami H-O, Ekbom A, et al. Physical activity and risk for breast cancer: a prospective cohort study among Swedish twins. *Int J Cancer*. 2002; 100:76-81.
21. Steenland K, Lowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I follow-up data: diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiol Biomarkers Prev*. 1995; 4:807-811.
22. Sesso HD, Paffenbarger RS Jr, Lee I-M. Physical activity and breast cancer risk in the College Alumni Health Study (United States). *Cancer Causes Control*. 1998;9:443-449.
23. Dorgan JF, Brown C, Barrett M, et al. Physical activity and risk of breast cancer in the Framingham Heart Study. *Am J Epidemiol*. 1994;139:662-669.
24. Moore DB, Folsom AR, Mink PJ, Hong CP, Anderson KE, Kushi LH. Physical activity and incidence of postmenopausal breast cancer. *Epidemiology*. 2000; 11:292-296.
25. Rockhill B, Willett W, Hunter DJ, Manson JE, Hankinson SE, Colditz GA. A prospective study of recreational physical activity and breast cancer risk. *Arch Intern Med*. 1999;159:2290-2296.
26. 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;9:681-687.
27. Carpenter CL, Ross RK, Paganini-Hill A, Bernstein L. Lifetime exercise activity and breast cancer risk among post-menopausal women. *Br J Cancer*. 1999; 80:1852-1858.
28. Coogan P F, Newcomb PA, Clapp RW, Trentham-Dietz A, Baron JA, Longnecker MP. Physical activity in usual occupation and risk of breast cancer (United States). *Cancer Causes Control*. 1997;8:626-631.
29. Siiteri PK. Adipose tissue as a source of hormones. *Am J Clin Nutr*. 1987;45:277-282.
30. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). *Cancer Causes Control*. 2001;12:47-59.
31. Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L. The acute versus the chronic response to exercise. *Med Sci Sports Exerc*. 2001; 33(6 suppl):S438-S445.
32. Morimoto L, White E, Zhao C, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative. *Cancer Causes Control*. 2002;13:741-751.
33. Chelbowski RT, Hendrix SL, Langer RD, et al, WHI Investigators. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA*. 2003;289:3243-3253.