

## Physical activity and risk of endometrial cancer in a prospective cohort study (United States)

Lisa H. Colbert<sup>1,\*</sup>, James V. Lacey Jr.<sup>2</sup>, Catherine Schairer<sup>2</sup>, Paul Albert<sup>3</sup>, Arthur Schatzkin<sup>2</sup> & Demetrius Albanes<sup>2</sup>

<sup>1</sup>Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, MD, USA; <sup>2</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; <sup>3</sup>Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA

Received 7 August 2002; accepted in revised form 16 March 2003

**Key words:** activity, cohort studies, endometrial cancer, exercise, physical fitness.

### Abstract

**Objective:** To examine the physical activity and endometrial cancer relationship in a prospective study of US women enrolled in the Breast Cancer Detection Demonstration Project (BCDDP) Follow-up Study.

**Methods:** We assessed past-year physical activity of all types in 23,369 women who returned the baseline questionnaire (1987–1989) and had no prior hysterectomy and/or endometrial cancer. Cox proportional hazards models were used to estimate age, education, and parity-adjusted rate ratios (RR) and 95% confidence intervals (CI) for the 253 confirmed endometrial cancer cases identified during an average 8.2 years of follow-up (ending 1995–1998).

**Results:** There were no dose–response relationships with either total or vigorous physical activity; however, compared to the lowest total activity quartile, the higher four quartiles had a non-significantly lower risk (RR = 0.8, CI = 0.6–1.0). The association with moderate activity varied with follow-up time: RRs (CI) for a 1 h increase in daily moderate activity within 2-year intervals of follow-up ( $\leq 2$ , 2.1–4.9, 5.0–8.0, > 8 years) were 1.1 (1.0, 1.2), 1.0 (0.9, 1.1), 1.0 (0.9, 1.1), and 0.8 (0.7, 1.0), respectively.

**Conclusion:** These data suggest that recent physical activity is not strongly related to the risk of endometrial cancer, and that prolonged exposure and longer follow-up may be necessary.

### Introduction

Evidence for an association between physical activity and endometrial cancer has been rather sparse and inconsistent. Of the 10 case–control and linkage studies that have examined the relationship, many showed lower risk among more active women, although the results were frequently neither statistically significant nor was there evidence of dose–response [1–10]. Two cohort investigations also provided data, one having

assessed occupational activity [11], and the other recreational activity [12], and both observed a reduced risk of endometrial cancer at increased activity levels during approximately 19–20 years of follow-up. A recent review noted that although the results to date point to a ‘probable’ association between physical activity and endometrial cancer, the number of studies evaluating this association are insufficient to draw definitive conclusions [13]. Mechanisms that have been hypothesized to mediate such an association include changes in obesity and/or fat mass as well as a reduced exposure to endogenous estrogen [14].

Methodological issues relevant to testing this hypothesis include the need to assess many types of activity, particularly household and leisure activities that may be important contributors among the middle-aged women evaluated in most studies. Some of the previous studies

\* Address correspondence to: Lisa H. Colbert, Gateway Building, Suite 3C-309, 7201 Wisconsin Ave., MSC 9205, Bethesda, MD 20892-9205, USA. Ph.: +1-301-496-1178; Fax: +1-301-496-4006; E-mail: lisa.colbert@att.net

† Lisa Colbert was supported by a Cancer Prevention Fellowship, National Cancer Institute.

have not modeled the association both with and without adjustment for body mass index (BMI) or body weight [2, 8, 9, 12], which may be important if, as has been suggested [13, 14], the activity–endometrial cancer association is mediated through altered body weight and resulting effects on hormonal profiles. Additionally, strong risk factors for endometrial cancer, such as hormone replacement therapy, must be carefully considered as potential confounders in these models [15].

We evaluated the association between physical activity and endometrial cancer in a cohort study of US women originally enrolled in the Breast Cancer Detection Demonstration Project (BCDDP). Activity of all types during the previous year was evaluated, and the analysis carefully considered potential confounding factors and effect modifiers of the association.

## Materials and methods

### *Study design and subjects*

The study subjects were participants in the BCDDP, a breast cancer screening program conducted in 27 cities throughout the US between 1973 and 1980. A follow-up study of a selected subset ( $n=64,182$ ) of the 283,222 BCDDP participants was initiated by the National Cancer Institute in 1979, and has been previously described [16]. The follow-up study included (1) all screening participants who underwent breast surgery during the screening period, but had no evidence of malignancy ( $n=25,114$ ); (2) all subjects who had recommendations by the project for surgical consultation, but did not have either a biopsy or aspiration performed ( $n=9628$ ); (3) all subjects diagnosed with breast cancer during the screening program ( $n=4275$ ) and (4) a sample of women who had neither surgery nor recommendation for surgical consultation during screening participation ( $n=25,165$ ). The follow-up study was approved by the Institutional Review Board at the National Cancer Institute, and informed consent was obtained from all participants.

Annual telephone interviews were conducted between 1979 and 1986, and one mailed questionnaire was self-administered during each of the following time periods: 1987–1989, 1993–1995, and 1995–1998. Pathology reports were sought for all self-reported cancers. In addition the cohort was periodically linked to the National Death Index to ascertain date and cause of death. Approximately 80% of the cohort was also linked to state cancer registries using the state of last known residence at the time of the 1995–1998 questionnaire mailing.

Information on physical activity habits was collected only in the 1987–1989 postal questionnaire, which is therefore used as the baseline for this analysis (from 7 to 16 years after participation in the original BCDDP screening program, and 8–10 years after the start of the follow-up study). This questionnaire also obtained information regarding smoking status, dietary habits, diabetes, and current body weight. Information on menstruation and menopause, including hysterectomy status, and hormone replacement therapy was collected on all questionnaires. Information on oral contraceptive use was obtained during the annual telephone interviews conducted between 1979 and 1986, while information on menarche, parity, and age at first live birth was collected on the baseline follow-up interview in 1979. Information on race, education, and income was collected on entry into the original screening program. For 213 women who did not report their body weight in the 1987–1989 questionnaire, weight measured during the screening program was used (Pearson correlation between reported weight on questionnaire and measured weight during the screening trial for all women was  $r=0.87$ ).

### *Physical activity assessment*

Participants were asked to estimate how many hours per typical weekday and weekend day in the past year they spent in each of four categories of activity by intensity: sleeping, light, moderate, and vigorous activity, and were instructed that the total for each day should add up to 24 h. Numerous examples of light, moderate, and vigorous activities that included occupational, leisure-time, household, and sports activities were listed on the questionnaire under the appropriate heading (*e.g.*, office work as a light activity, recreational tennis as a moderate activity, running as a vigorous activity). Acceptable ranges for reported hours by category were set at: sleep, 4–14; light, 0–20; moderate, 0–18, vigorous, 0–12; and total hours, 20–28. In order for the data to be considered valid, the sleep and total hours had to be in range, and the light, moderate, and vigorous hours had to be either in range or missing. If missing, a zero value was imputed. Women with invalid data were excluded from the analysis.

For women with valid physical activity data (see ‘analytical cohort’ below), the hours in each category of activity were then proportionalized to total 24 h/day. Weekly averages were obtained using the following formula:  $[(\text{weekday } h \times 5) + (\text{weekend } h \times 2)]/7$ . Substantially more women reported valid weekday data ( $n=42,684$ ) than weekend data ( $n=39,764$ ). Given the high correlation between the weekday and weekly

averages of activity (Spearman correlations: moderate activity,  $r=0.97$ ; vigorous activity,  $r=0.97$ ; total activity,  $r=0.96$ ; all  $p < 0.001$ ), the weekday data were used for this analysis under the assumption that it adequately represents regular, daily activity.

To examine total time spent in moderate and vigorous activity with consideration for intensity level, a Physical Activity Index (PAI) was created using literature-based relative metabolic equivalent unit (MET) values for moderate and vigorous activities [17]. MET values of four for moderate and seven for vigorous were used to create a weighted score [ $\text{MET-h/week} = (\text{h/week moderate activity} \times 4.0) + (\text{h/week vigorous activity} \times 7.0)$ ]. The analysis of the total physical activity and endometrial cancer relationship was also examined using both weekend and weekday data, in those who provided it.

#### Analytical cohort

Of the original 64,182 women invited into the follow-up study, 51,691 (84%) completed the 1987–1989 postal questionnaire, which contained information on physical activity. The 1987–1989 questionnaire was not completed by participants due to death ( $n=4605$ ), refusal to respond ( $n=2287$ ), illness ( $n=505$ ), or being otherwise unreachable or unavailable ( $n=5094$ ). Of the 51,691 who completed a questionnaire, 275 were previously diagnosed with endometrial cancer, and 22,959 had reported a hysterectomy that occurred before the date on which they completed the 1987–1989 questionnaire and were excluded from the analysis. Also excluded were women with unknown menopausal status ( $n=285$ ), those who never menstruated ( $n=8$ ), women with missing or invalid physical activity information ( $n=4599$ ), or those missing information on education, parity, or body weight ( $n=191$ ). A total of 23,374 participants were therefore available for this analysis, and they were predominantly white (88%). There were small percentages of black (3%), Hispanic (2%), and Asian American women (5%), along with those of other or unknown race/ethnicity (2%). The participants in the analysis were similar to the 38,054 from the follow-up who were excluded in regards to parity, body weight, and physical activity (for those who reported it). The excluded women were less likely to have used oral contraceptives (26 *versus* 32%) or have obtained at least some college education (41 *versus* 50%) while many more had used estrogen-only hormone replacement therapy (62 *versus* 38%). Additionally, they were more likely to have been diagnosed with breast cancer (7 *versus* 5%) or have had breast surgery with no malignant disease (41 *versus* 38%) and less likely to have been in the group not recommended for any

surgical procedure (38 *versus* 41%) in the original BCDDP study.

#### Case identification

Endometrial cancer cases were initially identified through self-reports, death certificates, or from searches in state cancer registries. Pathology reports were sought for all self-reported cases. Because the accuracy of self-reported diagnoses among those with pathology reports was not high (79%), cases supported only by self-reports were not considered cases in the main analyses. A total of 258 confirmed endometrial cancer cases were identified, of which five were determined to be of non-epithelial origin and excluded. Thus, 253 epithelial endometrial cancers were included in the final analysis; 182 (72%) based on pathology reports, 66 (26%) from state registries, and 5 (2%) from death certificates. Of the 253 cases, 94% were adenocarcinomas. Analyses were repeated including the 24 women who self-reported endometrial cancer, but for whom no confirmation was available.

#### Statistical analysis

Follow-up time began at the date of the 1987–1989 questionnaire that included physical activity, and ended at the earliest of the following dates: self-reported hysterectomy (5.6%), diagnosis of endometrial cancer (1.1%), death (7.9%), the date of completion of the last questionnaire, 1995–1998 (76.5%), date of last contact during 1995–1998 (2.5%), or, if status was otherwise unknown, the date at which the last questionnaire should have been completed (6.5%). Incident endometrial cancers were considered events, while individuals were censored for all other events noted.

Quintiles of total activity PAI were created based on the whole cohort. For daily hours spent in moderate and vigorous activities, categories of  $\leq 2$ , 2.1–4.9, 5.0–8.0, and  $> 8.0$ ; and 0, 0–1, 1.1–2, and  $> 2$  h; respectively, were created. The categories of moderate activity were approximate quartiles, while the vigorous activity categorization was chosen to allow comparison of smaller increments to no participation in vigorous activity. In our examination of moderate activity, women who reported any vigorous activity were excluded from the analysis in order to prevent potential confounding by vigorous activity.

Statistical analyses were performed using Statistical Analysis Systems (SAS) software (SAS Institute, Cary, NC). Cox proportional hazards models were used to estimate the rate ratios (RR) and 95% confidence

intervals (CI) of endometrial cancer associated with level of physical activity, with person-years of follow-up time as the underlying time metric. Likelihood ratio tests were used to test for overall effects, effect modification, and deviations from the proportional hazards assumption. All tests were two-sided and  $p < 0.05$  was used as the cut-off for statistical significance.

Covariate information was obtained from interviews up to and including the 1987–89 questionnaire on which physical activity was reported. All covariates shown in Table 2 were evaluated as confounders of the associations in addition to age at first live birth, race, a history of other cancers, duration of estrogen use, and menopausal status. Women were considered menopausal if they had not menstruated for at least three months prior to their baseline interview because of natural menopause or bilateral oophorectomy. Final models included age and variables (*i.e.*, parity and education) that produced a greater than 10% change in any of the  $\beta$ -coefficients for the physical activity variables.

As body weight may lie in the causal pathway of the physical activity–endometrial cancer association, sepa-

rate models were also run with adjustment for weight. Effect modification of the association between endometrial cancer and total activity was assessed by including variables and their cross-product terms in the models. Proportional hazards assumptions were assessed by including cross-product terms for physical activity and total follow-up time (person-years) in the models. There were no departures from the hazard assumptions for total PAI or vigorous activity, but the cross-product term was significant for follow-up time and moderate activity ( $p = 0.002$ ). Consequently, the association with moderate activity was assessed by estimating the RR for two-year intervals of follow-up time, and by looking at the risk estimates for quartiles of moderate activity in those with  $> 6$  years of follow-up.

## Results

The average follow-up time for the 23,369 study subjects was 8.2 years, with a maximum of 10.9 years and a minimum of less than a year. The women reported an

Table 1. Baseline characteristics of BCDDP participants by quintile of PAI, 1987–1998, US<sup>a,b</sup>

Characteristic <sup>c</sup>	PAI quintile (median MET-h/day <sup>b</sup> )				
	Q1 (8.0) n = 4617	Q2 (20.0) n = 4693	Q3 (32.0) n = 4560	Q4 (40.5) n = 4607	Q5 (56.0) n = 4892
Physical activity (h/day)					
Sleep	7.5 ± 1.2	7.6 ± 1.1	7.6 ± 1.0	7.5 ± 1.0	7.2 ± 1.0
Light	14.9 ± 1.7	11.7 ± 1.5	9.1 ± 1.4	7.3 ± 1.5	4.3 ± 1.9
Moderate	1.5 ± 1.1	4.2 ± 1.3	6.5 ± 1.6	7.7 ± 2.1	9.3 ± 3.3
Vigorous	0.1 ± 0.3	0.4 ± 0.6	0.7 ± 0.8	1.5 ± 1.2	3.0 ± 2.4
Age (years)	60.7 ± 8.6	61.6 ± 8.2	61.8 ± 7.8	61.8 ± 7.5	61.9 ± 7.6
Height (cm)	162.7 ± 6.9	162.5 ± 6.6	162.7 ± 6.5	162.4 ± 6.5	162.3 ± 6.4
Weight (kg)	66.7 ± 14.0	66.3 ± 13.0	65.9 ± 12.4	65.2 ± 11.9	64.6 ± 11.4
BMI (kg/m <sup>2</sup> )	25.2 ± 5.1	25.1 ± 4.7	24.9 ± 4.4	24.7 ± 4.3	24.5 ± 4.1
Education ≥ college (%)	58.5	52.9	49.8	48.7	42.7
Current smoker (%)	14.3	12.3	12.6	11.9	13.5
Age at menarche (years)	12.7 ± 1.4	12.8 ± 1.4	12.8 ± 1.4	12.8 ± 1.4	12.9 ± 1.5
Age at menopause (years)	49.9 ± 4.1	49.9 ± 4.2	49.9 ± 4.2	50.0 ± 4.0	49.8 ± 4.2
Parous (%)	81.8	83.8	86.7	86.3	87.6
OC use <sup>d</sup> (%)	36.1	32.4	31.5	30.5	28.6
Estrogen HRT use <sup>d</sup> (%)	35.7	38.2	37.7	39.2	36.7
Hypertension <sup>e</sup> (%)	2.9	2.9	3.0	3.0	2.5
Diabetes <sup>e</sup> (%)	5.8	4.9	4.1	4.0	4.0
Energy intake (kcal/day)	1275 ± 524	1280 ± 512	1292 ± 508	1295 ± 513	1296 ± 534
Fat intake (g/day)	51.1 ± 26.7	51.0 ± 26.7	50.8 ± 26.3	51.0 ± 26.5	50.8 ± 27.2
Alcohol intake (g/day)	0.43	0.24	0.22	0.22	0.04

<sup>a</sup> Values presented as mean ± standard deviation (SD) or % of group, with the exception of alcohol (median).

<sup>b</sup> The PAI was created using reported hours of moderate and vigorous activity/day and the approximate MET level for the type of activity reported: (moderate h × 4) + (vigorous h × 7).

<sup>c</sup> Abbreviations used: BMI – body mass index; OC – oral contraceptives; HRT – hormone replacement therapy.

<sup>d</sup> Reported ever using OC or estrogen-only HRT.

<sup>e</sup> Self-reported.

average of 9.5, 5.9, and 1.2 h/day of light, moderate, and vigorous activity, respectively. Baseline participant characteristics according to PAI quintile are shown in Table 1. Age, height, age at menarche, or age at menopause did not materially differ by level of total physical activity, while body weight and BMI decreased slightly with increasing level of activity. Women who reported more hours of moderate and vigorous physical activity were less likely to have attained higher levels of education, and slightly more likely to have borne children. Reported use of oral contraceptives decreased somewhat with increasing physical activity, while estrogen-replacement therapy was not related to activity level. Smoking, hypertension, and intake of energy and fat were not appreciably related to activity, while alcohol consumption and the proportion of women with diabetes were higher among the least active.

We examined the risk of endometrial cancer according to PAI quintile. There was no significant association between endometrial cancer and PAI adjusted for age, parity, and education, and there was no apparent dose response (Table 2). There were, however, non-statistically significant 10–30% lower RR in each of the four higher quintiles compared to the first. We compared the women in these four highest quintiles to those in the lowest quintile of activity and found an overall 20% reduction in risk that was of borderline significance (RR = 0.8; CI = 0.6, 1.0). Further adjustment for body weight did not appreciably change the quintile risk estimates (RR = 1.0, 0.8, 0.9, 0.8, 0.8 for quintiles 1–5, respectively), even though body weight itself was highly associated with endometrial cancer risk ( $p < 0.001$ ). There was no evidence for effect modification of the PAI association by age, weight, BMI, menopausal status,

parity, or reported use of estrogen-replacement therapy (data not shown). Including self-reported cases in the analysis (see Methods), yielded similar results (RR = 1.0, 0.7, 0.8, 0.7, 0.8 for quintiles 1–5, respectively;  $p_{\text{trend}} = 0.17$ ), as did the PAI calculated using both weekend and weekday data in those who provided it (RR = 1.0, 0.8, 0.7, 0.8, 0.8 for quintiles 1–5, respectively;  $p_{\text{trend}} = 0.26$ ). The analysis was also repeated excluding those women who came into the follow-up study with a history of breast cancer, and the results were similar (RR = 1.0, 0.8, 0.8, 0.7, 0.8 for quintiles 1–5, respectively;  $p_{\text{trend}} = 0.21$ ).

Amount of time spent in vigorous and moderate activities was also evaluated. Vigorous activity was not associated with endometrial cancer risk (Table 2), and further adjustment for body weight did not appreciably alter these results. Because the assumption of proportional hazards for hours of moderate activity was not met (*i.e.*, time \* moderate activity cross-product term,  $p = 0.002$ ), we examined the association by two-year intervals of follow-up time (Figure 1). There was a small, non-significant increase in risk associated with each 1 h per day increase in moderate activity during the first two years of follow-up, little association from two to eight years of follow-up, and lower risk with increased moderate activity after eight or more years of follow-up. The RR by quartile of activity during the complete follow-up were 1.0 (referent), 1.0 (0.6, 1.6), 0.8 (0.5, 1.3), and 0.8 (0.4, 1.3) for  $\leq 2$ , 2.1–4.9, 5.0–8.0, and  $> 8$  h of moderate activity/day, respectively ( $p_{\text{trend}} = 0.23$ ). Given the suggestion of a beneficial association with longer follow-up shown in Figure 1, we also examined quartiles of moderate activity among women with more than six years of follow-up only (six years was chosen to

Table 2. RRs (95% CI) of endometrial cancer by PAI<sup>a</sup> (total moderate and vigorous physical activity) and vigorous activity alone, BCDDP cohort, 1987–1998, US

	PAI quintile (median MET-h/day <sup>a</sup> )					$p_{\text{trend}}$
	Q1 (8.0)	Q2 (20.0)	Q3 (32.0)	Q4 (40.5)	Q5 (56.0)	
# Cases	60	47	51	45	50	
Person-years	36,942	38,332	37,427	37,963	40,525	
RR (CI) <sup>b</sup>	1.0	0.8 (0.5, 1.1)	0.9 (0.6, 1.2)	0.7 (0.5, 1.1)	0.8 (0.5, 1.1)	0.24
	Vigorous activity [h/day, median (range)]					
	0	1.0 (0.10–1.00)	2.0 (1.01–2.00)	4.0 (2.01–12.0)		
# Cases	124	57	29	43		
Person-years	91,981	41,061	26,841	31,305		
RR (CI) <sup>b</sup>	1.0	1.1 (0.8, 1.5)	0.8 (0.6, 1.2)	1.1 (0.7, 1.5)		0.94

<sup>a</sup> The PAI was created using reported hours of moderate and vigorous activity/day and the approximate MET level for the type of activity reported: (moderate h  $\times$  4) + (vigorous h  $\times$  7).

<sup>b</sup> Adjusted for age, parity, and education.

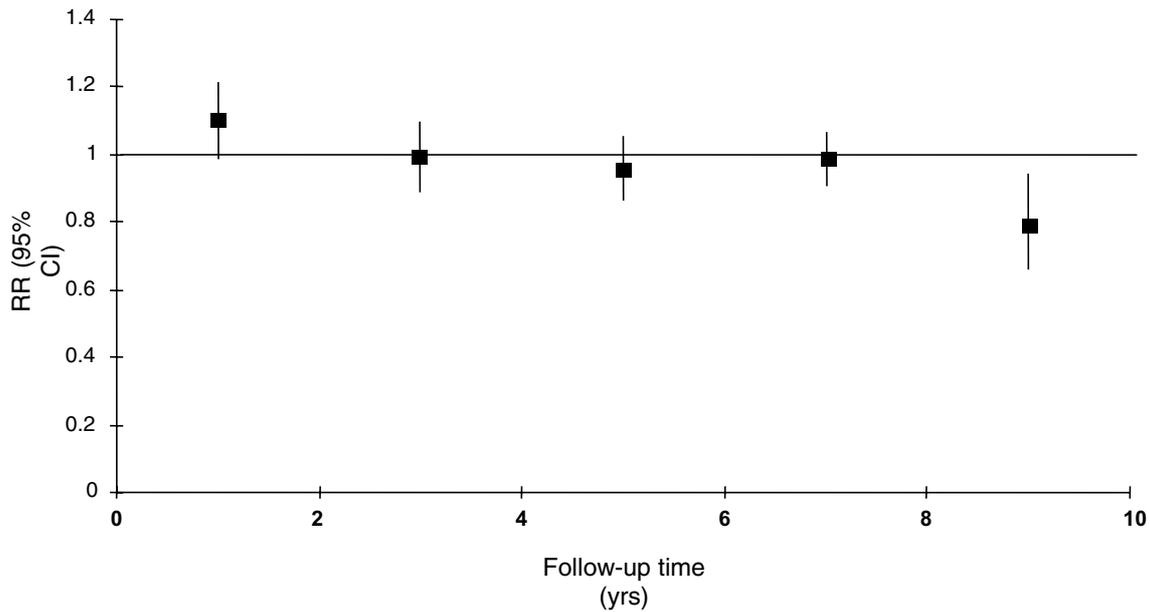


Fig. 1. RRs (95% CI) of endometrial cancer for moderate hours of physical activity by follow-up time, BCDDP cohort, 1987–1998, US. RR were calculated in 2-year intervals of follow-up ( $\leq 2$ ,  $> 2$ – $\leq 4$ ,  $> 4$ – $\leq 6$ ,  $> 6$ – $\leq 8$ , and  $> 8$  years) and represent the change in risk for each 1 h increase in moderate physical activity.

allow adequate cases in both time periods for the analysis). RR for the increasing quartiles were 1.0, 0.7, 0.7, and 0.3, but these estimates are based on only 53 cases for this restricted analysis.

## Discussion

In contrast to some previous cohort and case–control investigations, our prospective study did not find an overall association between average time spent in recent physical activity and the risk of developing endometrial cancer. We also saw no evidence of a dose–response relationship, with our estimates suggesting lower risk among those reporting any but the lowest level of activity, a potential threshold effect that was found on further categorical analysis to be of borderline statistical significance. While risk was somewhat decreased with increased time spent in moderate activities, this association only appeared in later years of follow-up. Additionally, vigorous activity was not related to endometrial cancer. Our results were not modified by BMI, weight, age, menopausal status, parity or use of estrogen-replacement therapy.

One possible interpretation of our finding of a modest risk reduction in women spending greater time in moderate activities that was evident only with longer follow-up time is that sustained, long-term participation

in such physical activity is necessary for a beneficial impact on endometrial cancer. The two previously published cohort studies of physical activity and endometrial cancer that found significant associations had substantially longer follow-up than did the present study ( $\sim 20$  versus  $\sim 8$  years) [11, 12]. Evidence regarding the importance of lifetime versus recent activity from case–control studies is mixed, with some showing larger inverse associations with more recent activity [2, 10], others supporting both recent and lifetime levels [3, 9], and one finding stronger associations with earlier life activity [7]. One issue complicating these time-related comparisons is that the past year physical activity assessed by such questionnaires can correlate with activity levels in preceding years in middle-aged women [18], such that the estimates reflect more than one period. Another possibility for the delayed association we noted is that the women who were more active at baseline may have been more likely to seek medical care if they were experiencing any unusual symptoms such as irregular bleeding, thus leading to a detection bias among the more active women. The stronger reduction in risk from moderate activity with prolonged follow-up may also simply be a chance finding.

The majority of prior studies have observed risk reductions of 30–40% for the highest average activity levels compared to lowest [13]. A lack of a dose–response relationship has been noted in some [4, 7, 10],

but not all [11, 12] studies. Other studies have shown significant associations between endometrial cancer and more moderate intensity activities compared to vigorous activities, as we did here. Levi *et al.* [2] found women who were sedentary *versus* most active in sports and leisure activities to have elevated risk of endometrial cancer (RR = 1.9, CI = 0.9, 4.0), but even higher risk estimates for women who were sedentary compared to the most active in housework (RR = 4.2, CI = 2.4, 7.5). Similarly, Sturgeon *et al.* [3] reported that RRs were higher for sedentary women compared to those actively engaged in housework than for sedentary women compared to those actively engaged in sports. It is not clear why greater levels of moderate, but not vigorous, activity might be associated with endometrial cancer.

Biologically, one would postulate that vigorous activity would afford greater inhibition of carcinogenesis than moderate activity, particularly if the association is mediated through a hormonal pathway. Cross-sectional data from postmenopausal women suggests that serum hormones such as androstenedione and estrone are lowest among women reporting the most activity [19], and in general, more intense activity or physical training is associated with more severe disruptions of menstrual function and/or hormone level [14]. This apparent inconsistency will require data from studies having more detailed activity data.

Given the variety of questionnaires that have been used to assess physical activity in studies of endometrial cancer, it is difficult to make comparisons between the level of activity in our participants *versus* those in prior studies. The women in our study reported relatively high levels of daily activity. Compared to data from the Behavioral Risk Factor Surveillance System (BRFSS) in 1990, for example, which found that only 24% of US women ages 18 and older get at least 30 min of moderate leisure-time activity most days of the week or at least 20 min of vigorous activity three days/week [20], our study participants reported significantly more activity. In the study by Littman *et al.* [10], only 11% of their similarly aged women reported more than 6 h per week of any leisure-time physical activity. The difference in these reports may be due to the fact that BRFSS and Litman *et al.* [10] queried only leisure-time activity. Greater overall levels of activity may have resulted from our questionnaire's intentional inclusion of household activities, important when assessing the activity of women in particular [21].

Data in Table 1 show that the more active women in this cohort tended to have had less education, were more likely to have had children, drank less alcohol, and were only slightly leaner than the less active women, patterns generally opposite those observed for higher levels of

leisure exercise or recreational activity [22]. This suggests that our study subjects may have been reporting more housework, or less likely, occupational activity, although we are unable to determine this from the format of the questionnaire we used. It is also possible that our cohort of women, who were initially enrolled in a breast cancer screening trial in the 1970s and responded to our activity questionnaire in the late 1980s, may have been more health conscious and active than women sampled in BRFSS. That the reported body weights and BMIs of the BCDDP women were quite low is consistent with greater activity and health consciousness (but may also have resulted from the necessary exclusion of women with prior hysterectomy). It is also possible, however, that over-reporting contributed to some of the daily averages of 1.2 vigorous hours and 5.9 moderate hours of activity observed. For example, our physical activity questionnaire instructed the women to account for 24 h of total daily activity, including sleep. Having been incorporated into a broader BCDDP mailed questionnaire, the activity questions were self-administered, which may have resulted in the inflation of the reported time spent in more strenuous activity levels compared to more open-ended, interviewer-administered questionnaires [23].

Strengths of our study include its prospective design, cohort size, and the relatively large number of cases for analysis. The activity instrument queried typical weekend and weekday activities including occupational, recreational, and housework activities. We were also able to use updated information on hysterectomies, which was accurately reported by BCDDP women [24], to censor those who were no longer at risk during the course of follow-up, and were able to assess numerous potential confounding factors in our analyses. As in many studies of physical activity and cancer, few factors, including body weight, were found to empirically confound our data [14].

Our analysis is limited by the fact that the BCDDP Follow-up Study was not conducted specifically to evaluate physical activity in relation to endometrial cancer. These results may not generalize to the US population as a whole, as these were women who volunteered to participate in the original BCDDP study and agreed to continue in the follow-up study, in which those with prior breast cancers and biopsies were over-sampled. It is possible that the women in our analysis who had breast cancer and/or breast surgery many years prior to physical activity ascertainment may have altered their physical activity patterns following those diagnoses and treatment; however, our study was focused on activity during the previous year, and so our results should not have been biased in this respect. Further, our

results were unchanged when we excluded women with breast cancer, suggesting that the results are internally valid. Another potential limitation is that the sample we used for analysis excluded women who had more breast surgical procedures, had a higher prevalence of estrogen use, and were less educated, which may have resulted in a sample with endometrial cancer risk that was different from that in the original population sample. Importantly, the physical activity level in those who were excluded (which was available for most of the women) was similar to the level of those included in the study, suggesting that our results were not materially biased by these exclusions. Although our questionnaire was designed to capture typical activity of all types, its necessary simplicity restricted our ability to examine activity by subtype, and the format may have resulted in some over-reporting of activity. Additionally, measurement error in our questionnaire may have attenuated the risk estimates we observed.

In contrast to many previously published studies, we observed no significant overall relationship between physical activity and endometrial cancer in this study. We did, however, observe a 20% lower risk among women who were engaged in any but the lowest level of total physical activity, and a lower risk for higher moderate physical activity in particular, but only with longer follow-up. Future studies designed to directly address the role of detailed components of physical activity and periods of exposure in the development of endometrial and other women's cancers should help clarify the associations. In particular, the potential difference between long-term *versus* recent activity on endometrial cancer should be further explored.

### Acknowledgements

We are indebted to the Breast Cancer Detection Demonstration Project study participants, Leslie Carroll and Lisa Kahle of IMS Inc., Rockville, MD for database and statistical support, and to Susan Englehart, Catherine Ann Grundmayer and the other staff at Westat, Inc., Rockville, MD, for the conduct of the Breast Cancer Detection Demonstration Project Follow-up Study. We acknowledge the California Department of Health Services, Cancer Surveillance Section; the Florida Cancer Data System under contract to the state Department of Health; the Maryland Cancer Registry, Maryland Department of Health and Mental Hygiene; the Michigan Cancer Surveillance Program within the Division for Vital Records and Health Statistics, Michigan Department of Community Health; the Division of Health Statistics, Pennsylvania Depart-

ment of Health; the Tennessee Cancer Registry; the Texas Department of Health; and the states of Arizona, Georgia, Hawaii, Idaho, Iowa, New Jersey, New York, North Carolina, Ohio, Oregon, and Rhode Island for providing data from their cancer registries for use in these analyses. The views expressed in this paper are solely those of the authors and do not necessarily reflect the opinions of any state agency listed above.

### References

- Zheng W, Shu X, McLaughlin J, Chow W-H, Gao Y-T, Blot W (1993) Occupational physical activity and the incidence of cancer of the breast, corpus uteri, and ovary in Shanghai. *Cancer* **71**: 3620–3624.
- Levi F, La Vecchia C, Negri E, Franceschi S (1993) Selected physical activities and the risk of endometrial cancer. *Br J Cancer* **67**: 846–851.
- Sturgeon S, Brinton L, Berman M, et al. (1993) Past and present physical activity and endometrial cancer risk. *Br J Cancer* **68**: 584–589.
- Shu X, Hatch M, Zheng W, Gao Y, Rinton L (1993) Physical activity and risk of endometrial cancer. *Epidemiology* **4**: 342–349.
- Hirose K, Tajima K, Hamajima N, et al. (1996) Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. *Jpn J Cancer Res* **87**: 1001–1009.
- Goodman M, Hankin J, Wilkens L, et al. (1997) Diet, body size, physical activity, and risk of endometrial cancer. *Cancer Res* **57**: 5077–5085.
- Olson S, Vena J, Dorn J, et al. (1997) Exercise, occupational activity, and risk of endometrial cancer. *Ann Epidemiol* **7**: 46–53.
- Salazar-Martínez E, Lazcano-Ponce E, Lira-Lira G, et al. (2000) Case-control study of diabetes, obesity, physical activity and risk of endometrial cancer among Mexican women. *Cancer Causes Control* **11**: 707–711.
- Moradi T, Weiderpass E, Signorello L, Persson I, Nyren O, Adami H-O (2000) Physical activity and postmenopausal endometrial cancer risk (Sweden). *Cancer Causes Control* **11**: 829–837.
- Littman A, Voigt L, Beresford S, Weiss N (2001) Recreational physical activity and endometrial cancer risk. *Am J Epidemiol* **154**: 924–933.
- Moradi T, Nyren O, Bergstrom R, et al. (1998) Risk for endometrial cancer in relation to occupational physical activity: a nationwide cohort study in Sweden. *Int J Cancer* **76**: 665–670.
- Terry P, Baron J, Weiderpass E, Yuen J, Lichtenstein P, Nyren O (1999) Lifestyle and endometrial cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer* **82**: 38–42.
- Friedenreich C (2001) Physical activity and cancer prevention: from observational to intervention research. *Cancer Epidemiol Biomarkers Prev* **10**: 287–301.
- McTiernan A, Ulrich C, Slate S, Potter J (1998) Physical activity and cancer etiology: associations and mechanisms. *Cancer Causes Control* **9**: 487–509.
- Pike M, Peters R, Cozen W, et al. (1997) Estrogen-progestin replacement therapy and endometrial cancer. *J Natl Cancer Inst* **89**: 1110–1116.
- Schairer C, Byrne C, Keyl P, Brinton L, Sturgeon S, Hoover R (1994) Menopausal estrogen and estrogen-progestin replacement

- therapy and risk of breast cancer (United States). *Cancer Causes Control* **5**: 491–500.
17. Ainsworth B, Haskell W, Leon A, *et al.* (1993) Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* **25**: 71–80.
  18. Fortier M, Katzmarzyk P, Malina R, Bouchard C (2001) Seven-year stability of physical activity and musculoskeletal fitness in the Canadian population. *Med Sci Sports Exerc* **33**: 1905–1911.
  19. Madigan M, Troisi R, Potischman N, Dorgan J, Brinton L, Hoover R (1998) Serum hormone levels in relation to reproductive and lifestyle factors in postmenopausal women (United States). *Cancer Causes Control* **9**: 199–207.
  20. Centers for Disease Control (2001) *MMWR* **50**: 166–169.
  21. Ainsworth B (2000) Challenges in measuring physical activity in women. *Exercise Sport Science Rev* **28**: 93–96.
  22. Britton J, Gammon M, Kelsey J, *et al.* (2000) Characteristics associated with recent recreational exercise among women 20–44 years of age. *Women Health* **31**: 81–96.
  23. Sallis J, Saelens B (2000) Assessment of physical activity by self-report: status, limitations, and future directions. *Res Quart Exercise Sport* **71**: 1–14.
  24. Brinton L, Hoover R, Szklo M, Fraumeni Jr J (1981) Menopausal estrogen use and risk of breast cancer. *Cancer* **47**: 2517–2522.