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Long-term and baseline recreational physical activity and risk of endometrial cancer: the California Teachers Study

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Background: Physical activity may be associated with decreasing endometrial cancer risk; it remains unclear whether the association is modified by body size.

Methods: Among 93 888 eligible California Teachers Study participants, 976 were diagnosed with incident endometrial cancer between 1995–1996 and 2007. Cox proportional hazards regression methods were used to estimate relative risks (RRs) and 95% confidence intervals (CIs) for endometrial cancer associated with long-term (high school through age 54 years) and baseline (3 years prior to joining the cohort) strenuous and moderate recreational physical activity, overall and by body size.

Results: Increased baseline strenuous recreational physical activity was associated with decreased endometrial cancer risk ($P_{trend} = 0.006$) with approximately 25% lower risk among women exercising >3 h per week per year than among those exercising $<1/2$ h per week per year (RR, 0.76; 95% CI, 0.63–0.92). This inverse association was observed among overweight/obese women (body mass index $\geq 25\,kg\,m^{-2}$; $P_{trend} = 0.006$), but not among thinner women ($P_{trend} = 0.12$). Baseline moderate activity was associated with lower risk among overweight/obese women.

Conclusion: Increasing physical activity, particularly strenuous activity, may be a lifestyle change that overweight and obese women can implement to reduce their endometrial cancer risk.

Endometrial cancer is the most common gynaecological malignancy and the fourth most frequent cancer diagnosis of women in developed countries, accounting for 6% of all new cancer cases among women in the United States (Jemal *et al*, 2008). Established risk factors for endometrial cancer include obesity, diabetes mellitus, use of unopposed oestrogen therapy, family history of endometrial cancer, nulliparity, earlier age at menarche and later age at menopause (Gruber and Thompson, 1996; McPherson *et al*, 1996; Kaaks *et al*, 2002). One potential modifiable risk factor related to obesity is physical activity. Studies investigating the association between physical activity and endometrial cancer risk have been mixed; some cohort (Zheng *et al*, 1993; Moradi *et al*, 1998; Terry *et al*, 1999; Schouten *et al*, 2006) and case–control studies (Salazar-Martinez *et al*, 2000; Matthews *et al*, 2005; John *et al*, 2010) have suggested that higher levels of physical activity decrease endometrial cancer risk, while other studies have reported no evidence for such an association (Colbert *et al*, 2003; Furberg and Thune, 2003; Friberg *et al*, 2006; Friedenreich *et al*, 2007).

Two recent reviews concluded that endometrial cancer risk was reduced approximately 20–40% in women with the highest level of physical activity (Cust *et al*, 2007; Voskuil *et al*, 2007). Owing to the diversity of physical activity assessments used in prior studies,

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additional studies using detailed, standardised physical activity assessments are needed to confirm these findings and address remaining questions such as the type, intensity and timing of physical activity that is most effective in reducing endometrial cancer risk.

We investigated the association between physical activity and endometrial cancer in the prospective California Teachers Study (CTS) cohort, using information reported on the baseline (enrolment) CTS questionnaire about strenuous and moderate recreational physical activity during several extended time periods throughout participants' lives. Further, we examined whether body mass index (BMI; kg m^{-2}) at baseline modified any observed association between physical activity and endometrial cancer risk.

MATERIALS AND METHODS

Study population. A detailed description of the CTS has been published previously (Bernstein *et al*, 2002). In brief, the CTS is a prospective cohort of current, recently employed, and retired female public school teachers, administrators and other professionals who were vested members of the California State Teachers Retirement System in 1995. Cohort participants completed a baseline questionnaire in 1995–1996 that collected information on personal medical history, family history of cancer, reproductive factors, medication and hormone use, and lifestyle factors such as recreational physical activity, diet, alcohol intake and smoking history. Use of human subjects' data in this study was approved by the Institutional Review Board at each collaborating institution as well as the California Committee for the Protection of Human Subjects in accord with assurances approved by the US Department of Health and Human Services.

A total of 133 479 participants comprised the entire CTS cohort. For this analysis, we excluded, in sequence, participants who, at baseline, lived outside of California ($n=8867$), had a prior or unknown history of any cancer ($n=2284$), limited their participation to breast cancer research ($n=18$), reported having had a hysterectomy ($n=27\,794$), had missing data on physical activity ($n=594$), or had invalid physical activity responses ($n=34$). The resulting cohort for this analysis consisted of 93 888 participants. Participants with missing data on BMI ($n=3537$) were excluded from analyses of effect modification by BMI.

Case ascertainment and Follow-up. Incident diagnoses of endometrial cancer were identified through annual linkage with the California Cancer Registry (CCR). The CCR is a population-based cancer registry established by state legislation mandating cancer reporting; the CCR is estimated to be over 99% complete (Kwong *et al*, 2001). The high standards maintained by the CCR ensure that follow-up for cancer outcomes are virtually complete as long as cohort members reside in California. Linkage between the CTS cohort and the CCR database is based on full name, date of birth, address and social security number and includes manual review of possible matches. California and national mortality files were used to ascertain date and cause of death. Follow-up time was calculated as the number of days between the date of baseline questionnaire completion and the first occurrence of a first diagnosis of endometrial cancer. The end date of follow-up is defined as the date of endometrial cancer diagnosis, date of a move for >4 months out of California, date of death – or the end date of follow-up – whichever came first.

A total of 997 incident cases of endometrial cancer were diagnosed between baseline and end of follow-up on 31 December 2007, including 840 women with type 1 endometrial cancers (International Classification of Diseases for Oncology-3 (ICD-O-3) histology codes 8050, 8140, 8210, 8260, 8323, 8380, 8382, 8480, 8481, 8560, 8570), 53 women with type 2 endometrial cancers (ICD-O-3 histology codes 8255, 8310, 8441, 8460, 8461), 83 women with other histology codes (ICD-O-3 histology codes 8950, 8951, 8980, 8890, 8896, 8930, 8933 or other).

Measures of recreational physical activity. Participants provided detailed information on the baseline questionnaire regarding their recreational physical activity during various time periods in their lives. These time periods included: while in high school, between the ages of 18–24, 25–34, 35–44 and 45–54 years, and during the 3 years before completing the questionnaire, herein referred to as 'baseline' activity. For each time period, participants were asked to indicate the average amount of time spent participating in strenuous intensity physical activity (e.g., swimming laps, aerobics/calisthenics, running and jogging) and moderate-intensity activity (e.g., brisk walking, recreational tennis, golf, softball and volleyball). Participants reported the average number of hours per week (none, 0.5, 1, 1.5, 2, 3, 4–6, 7–10, and $\geqslant$11 h per week) and average number of months per year (1–3, 4–6, 7–9 and 10–12 months per year) for each level of physical activity intensity in which they participated. For each time period and intensity level, the average annual hours per week was multiplied by months per year of participation and divided by total years to estimate average hours per week per year. The midpoint value of the hours per week and months per year categories was assigned, when appropriate, in making these calculations. A conservative value of 12 was assigned to the category $\geqslant$11 h per week. Long-term recreational physical activity was calculated by multiplying the average hours per week per year for each time period by the number of total years spent in that time period. These values were then summed across all time periods and divided by the total number of years. Long-term average annual strenuous recreational physical activity and long-term average annual moderate recreational physical activity were then categorised into approximate quartiles ($\leqslant$0.50, 0.51–1.50, 1.51–2.99, $>$3.00 hours per week per year). Recent physical activity was calculated in a manner similar to that outlined for long-term activity, by calculating the average hours per week per year of strenuous and moderate physical activity for the 3 years prior to cohort enrolment (baseline).

A combined strenuous plus moderate physical activity variable was created for long-term recreational physical activity and for baseline recreational physical activity by summing the hours per week per year of strenuous recreational physical activity and hours per week per year of moderate recreational physical activity, and categorising the total into approximate quartiles based on person-years ($\leqslant$0.50, 0.51–2.59, 2.60–5.49, $>$5.00 hours per week per year).

Assessment of endometrial cancer risk factors. Information on other potential endometrial cancer risk factors was collected in the baseline questionnaire, including race and ethnicity, personal and family history of endometrial cancer, hormone therapy (HT) use, oral contraceptive use, reproductive history, menopausal status, height, weight, and history of other cancers and conditions including diabetes (Bernstein *et al*, 2002). Body mass index was categorised into six groups: $<$20, 20.0–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, $\geqslant$35 kg m^{-2} or unknown.

Participants reporting ongoing menstrual periods, who had never used hormones for menopausal symptoms, were considered premenopausal. Participants were classified as perimenopausal if their periods had stopped within the 6 months prior to completing the baseline questionnaire and they were not currently pregnant, and as postmenopausal if they met any of the following criteria: (1) their periods stopped for $>$6 months, (2) they had a bilateral oophorectomy, (3) they were of age 56 years or older at baseline and not already classified as premenopausal or perimenopausal or (4) they started using HT to treat menopausal symptoms before their periods stopped. Hormone therapy use at the time of cohort entry was characterised with respect to pattern of HT use over time and formulations used (oestrogen alone or oestrogen–progestin combination). Menopausal status and HT use were combined to create a six category variable: premenopausal, postmenopausal/never used HT, postmenopausal/used only unopposed oestrogen, postmenopausal/used only an oestrogen plus progesterone formulation, postmenopausal/used both unopposed oestrogen and oestrogen plus progesterone formulations, and unknown as to menopausal status or HT use status. Perimenopausal participants were combined with premenopausal participants for the analyses described here.

Statistical analyses. Multivariable Cox proportional hazards regression methods were used to estimate the hazard rate ratios, presented as a relative risks (RRs) and 95% confidence intervals (CIs), for the association between exposures of interest and risk of endometrial cancer, using ages at start and end of follow-up (in days) to define time on study. All models were stratified by age at baseline (in single years of age) and models were adjusted for race (white, Non-white). In addition, we examined the potential confounding effects of relevant risk factors including family history of endometrial cancer, age at menarche, oral contraceptive use, menopausal status/HT use, number of full-term pregnancies, number of total pregnancies, BMI, smoking history, alcohol intake, history of hypertension and history of diabetes. Each factor was added to the race-adjusted model to determine whether its inclusion changed the magnitude of the main effect association. We then included potential confounding variables in a single model to assess their combined effect on the association between physical activity and endometrial cancer risk. With the exception of BMI, none of the potential confounding factors affected the association, either alone or in combination. Therefore, only BMI was included as a potential confounder in the final model. The two physical activity variables, strenuous physical activity and moderate physical activity, were mutually adjusted for each other in the models examining the association between these physical activity measures and endometrial cancer risk.

To assess the proportional hazards assumption using physical activity variables (long-term, recent; strenuous, moderate, and strenuous plus moderate intensities), we first visually examined whether Kaplan–Meier survival curves had parallel lines (Therneau, 1996). We also plotted scaled Schoenfeld residuals by time to test for a zero slope and tested the null hypothesis of no correlation between the residuals and time on study (Schoenfeld, 1982). No evidence for a violation of the proportional hazards assumption was apparent.

Trend tests for each physical activity variable were performed by fitting the median value of exposure categories in the statistical models and determining whether the estimated slope coefficient differed from zero (Wald test). We evaluated effect modification by BMI (<25, $\geqslant 25\,\text{kg}\,\text{m}^{-2}$) by constructing likelihood ratio tests that assessed homogeneity of trends across categories of the potential effect modifier. Two-sided *P*-values are reported for tests for trend and for homogeneity of trends. We did not adjust CIs or *P*-values for multiple comparisons. All statistical analyses were performed using the SAS software program (SAS version 9.2; SAS Institute, Cary, NC, USA).

RESULTS

The median follow-up time for the 93 888 participants in this study is 12.1 years. The mean age at diagnosis was 66.9 years (s.d. ± 10.9 years) for the 976 women diagnosed with endometrial cancer during follow-up and median time to diagnosis was 5.8 years. Table 1 presents age-adjusted percentages for selected baseline characteristics of women included in the analytic cohort by category of baseline strenuous recreational physical activity.

Baseline recreational physical activity appeared to be more strongly associated with endometrial cancer risk than long-term recreational physical activity. Baseline strenuous recreational physical activity was inversely associated with endometrial cancer risk ($P_{\text{trend}} = 0.006$) with approximately a 24% decrease in risk comparing participants with the highest to those with the lowest activity level (RR >3.00 *vs* $\leqslant 0.50$ hours per week per year, 0.76; 95% CI, 0.63–0.92, Table 2). Among all participants, all long-term activity measures, as well as baseline moderate and baseline strenuous plus moderate activity, were modestly, although not statistically significantly, associated with endometrial cancer risk. We evaluated the risk of associations of strenuous as well as moderate long-term activity within each of the age periods from high school to age 54 years that were studied, restricting the analysis to women who could contribute to all age periods; the results were similar within each of the age periods and we could not identify a particular age period when physical activity had the greatest impact (data not shown here).

Baseline strenuous recreational physical activity was associated with endometrial cancer risk among women who were at least $25\,\text{kg}\,\text{m}^{-2}$ at baseline ($P_{\text{trend}} = 0.006$), but was not associated with risk among women with a lower BMI ($P_{\text{trend}} = 0.12$; Table 3). Among the most active women with BMI $\geqslant 25\,\text{kg}\,\text{m}^{-2}$ relative to those with the least activity (<0.50 hours per week per year), risk was reduced 39% (RR, 0.61; 95% CI, 0.43–0.85). No other associations were observed when data were stratified by BMI. Body mass index at baseline ($<25\,\text{kg}\,\text{m}^{-2}$ *vs* $\geqslant 25\,\text{kg}\,\text{m}^{-2}$) did not modify any of the associations between recreational physical activity and endometrial cancer risk. Further, associations between physical activity and endometrial cancer risk also did not differ by menopausal status, use of HT, smoking status and OC use (data not shown here).

In addition, for all previously described analyses, we restricted the endometrial cancer case definition to participants with type 1 endometrial cancers. Results did not differ from those described and therefore are not presented.

DISCUSSION

The present cohort study is one of only a few studies (Gierach *et al*, 2009; John *et al*, 2010) that has assessed endometrial cancer risk in relation to long-term and baseline physical activity by multiple intensity levels. We observed a strong inverse association between baseline strenuous physical activity and risk. Baseline moderate activity alone was not associated with endometrial cancer risk. Our findings further suggest that overweight and obese women may derive the greater benefit from baseline strenuous recreational physical activity than leaner women, although we were unable to demonstrate any effect modification by BMI.

To date, studies of different designs have examined the relationship between physical activity and endometrial cancer risk, including linkage (Pukkala *et al*, 1993; Zheng *et al*, 1993), prospective cohort (Moradi *et al*, 1998; Terry *et al*, 1999; Moradi *et al*, 2000; Colbert *et al*, 2003; Furberg and Thune, 2003; Schouten *et al*, 2004; Friberg *et al*, 2006; Friedenreich *et al*, 2007; Patel *et al*, 2008; Conroy *et al*, 2009; Gierach *et al*, 2009), population-based case–control (Shu *et al*, 1993; Sturgeon *et al*, 1993; Goodman *et al*, 1997; Olson *et al*, 1997; Littman *et al*, 2001; Matthews *et al*, 2005; John *et al*, 2010) and hospital-based case–control (Dosemeci *et al*, 1993; Levi *et al*, 1993; Hirose *et al*, 1996; Kalandidi *et al*, 1996; Troisi *et al*, 1997; Salazar-Martinez *et al*, 2000; Tavani *et al*, 2009) studies. However the type, time points and intensity of physical activity have varied across these studies. A number of prospective

Table 1. Distribution of selected age-adjusted baseline characteristics among 93 888 California Teachers Study participants, under follow-up for endometrial cancer from baseline (c. 1995–1996) through 31 December 2007, by category of baseline strenuous recreational physical activity

			Baseline strenuous recreational physical activity (hours per week per year)[a]			
Baseline characteristics	***n* (cases)**	**Person-years**	**⩽0.50, %**	**0.51–1.50, %**	**1.51–3.00, %**	**>3.00, %**
Total participants	93 888		55.5	15.4	7.3	21.8
Endometrial cancer cases	976		66.8	13.3	5.9	13.9
Age (years)[b]						
20–29	5364 (2)	58 051	35.8	21.9	10.5	31.8
30–39	15 543 (17)	175 075	42.5	19.3	9.7	28.5
40–49	28 040 (153)	322 019	53.2	16.9	7.8	22.1
50–59	21 653 (303)	241 276	60.6	13.9	6.4	19.1
60–69	12 552 (286)	135 694	63.1	11.7	5.7	19.5
70–79	7579 (156)	75 933	68.5	10.0	4.7	16.8
⩾80	3 157 (59)	23 410	78.7	8.7	3.5	9.2
Race						
White	80 830 (876)	885 873	54.7	15.7	7.4	22.1
Non-white	13 058 (100)	145 587	57.9	15.7	7.1	19.3
Body mass index ($kg\,m^{-2}$)						
<25	56 954 (436)	628 560	49.5	15.8	8.0	26.7
25–29.9	21 407 (269)	235 520	60.6	16.3	7.1	16.1
⩾30	11 990 (224)	131 742	70.9	14.7	5.2	9.3
Unknown	3537 (47)	35 638	60.4	14.4	6.2	19.0
Body mass index ($kg\,m^{-2}$)						
<20	10 584 (71)	115 815	48.4	16.0	8.1	27.5
20–22	30 344 (211)	335 739	47.6	15.7	8.2	28.5
23–24	16 026 (154)	177 005	53.8	16.1	7.5	22.6
25–29	21 407 (269)	235 520	60.6	16.3	7.1	16.1
30–34	7624 (108)	84 027	67.7	15.6	5.9	10.8
35 +	4366 (116)	47 715	76.2	13.0	4.1	6.6
Unknown	3537 (47)	35 638	60.4	14.4	6.2	19.0
Menopausal status						
Peri- or premenopausal	50 289 (239)	570 082	50.9	17.3	8.2	23.6
Postmenopausal	38 337 (692)	402 025	62.6	12.7	5.9	18.8
Unknown	5262 (45)	59 352	58.4	15.4	6.8	19.5
Smoking status						
Never	63 133 (607)	698 187	55.3	16.0	7.5	21.3
Former	25 599 (314)	278 774	53.8	15.2	7.2	23.8
Current	4661 (51)	49 324	60.7	15.5	6.5	17.3
Unknown	495 (4)	5174	58.3	13.9	6.8	21.0
# Full-term pregnancies						
Never pregnant	20 338 (221)	221 227	50.7	16.0	7.6	25.8
0	6124 (44)	67 235	44.9	17.1	8.7	29.3
1–4	63 340 (657)	699 880	57.2	15.6	7.2	20.0
5–9	2007 (30)	21 540	65.2	13.8	5.7	15.3
10 +	21 (0)	223	64.1	10.2	0	25.6
Unknown	2058 (24)	21 354	55.7	15.0	6.6	22.7
# Full-term pregnancies						
Never pregnant	20 338 (221)	221 227	50.7	16.0	7.6	25.8
0	6124 (44)	67 235	44.9	17.1	8.7	29.3
1	15 073 (117)	164 835	54.3	16.6	8.0	21.1
2	29 999 (303)	334 211	57.2	15.4	7.3	20.2
3	13 637 (182)	150 321	59.1	15.4	6.9	18.6
4 +	6659 (85)	72 277	62.8	13.8	5.3	18.1
Unknown	2058 (24)	21 354	55.7	15.0	6.6	22.7

Table 1. (Continued)

			Baseline strenuous recreational physical activity (hours per week per year)[a]			
Baseline characteristics	*n* (cases)	Person-years	⩽0.50, %	0.51–1.50, %	1.51–3.00, %	>3.00, %
Family history of endometrial cancer						
No	88 224 (910)	970 388	55.1	15.7	7.4	21.7
Yes	2638 (39)	28 706	55.7	15.0	6.8	22.5
Unknown	3026 (27)	32 365	56.0	16.4	6.3	21.3

Abbreviations: # = number; BMI = body mass index.
[a]Values are presented as % of participants who participate in the respective level of physical activity and who represent the specific baseline characteristic category.
[b]Unadjusted values presented.

Table 2. Adjusted[a] relative risks (RRs) and 95% confidence intervals (CIs) for the risk of incident invasive endometrial cancer associated with long-term and baseline recreational physical activity among 93 888 California Teachers Study women between 1995 and 2007

	Long-term physical activity by intensity (hours per week per year)			Baseline physical activity by intensity (hours per week per year)		
	Person-years	Cases, *n*	RR[a] (95% CI)	Person-years	Cases, *n*	RR[a] (95% CI)
Strenuous[b]						
⩽0.50	282 940	385	1.00 (reference)	567 481	652	1.00 (reference)
0.51–1.50	242 240	248	1.01 (0.86–1.19)	160 423	130	1.01 (0.83–1.22)
1.51–2.99	229 105	171	0.90 (0.75–1.10)	75 669	58	1.00 (0.76–1.32)
⩾3.00	277 173	172	0.92 (0.75–1.13)	227 887	136	0.76 (0.63–0.92)
P_{trend}			0.31			0.006
Moderate[b]						
⩽0.50	209 732	247	1.00 (reference)	339 043	352	1.00 (reference)
0.51–1.50	262 605	258	1.04 (0.87–1.24)	240 829	210	1.01 (0.85–1.21)
1.51–2.99	262 243	239	1.05 (0.87–1.26)	121 632	97	0.96 (0.76–1.21)
⩾3.00	296 878	232	0.91 (0.75–1.11)	329 955	317	1.01 (0.86–1.19)
P_{trend}			0.24			0.87
Strenuous plus moderate						
⩽0.50	90,597	134	1.00 (reference)	229 005	270	1.00 (reference)
0.51–2.59	307,874	351	1.03 (0.84–1.26)	294 736	283	1.01 (0.85–1.20)
2.60–5.49	320,794	282	1.00 (0.81–1.23)	268 501	246	0.95 (0.80–1.14)
⩾5.5	312,193	209	0.85 (0.68–1.06)	239 217	177	0.84 (0.69–1.02)
P_{trend}			0.03			0.05

[a]RRs are from multivariable Cox proportional hazards regression models using age (in days) as the time metric and stratified by age (in years) with the adjustment for race and body mass index (BMI; using the following BMI categories: <20; 20–22.9; 23–24.9; 25–29.9; 30–34.9; 35+ kg m^{-2}). Trends are fit to the median for each category.
[b]Both moderate physical activity and strenuous physical activity variables are fit simultaneously in a single model.

cohort studies have found an inverse association between recreational physical activity and endometrial cancer risk (Sturgeon *et al*, 1993; Terry *et al*, 1999; Furberg and Thune, 2003; Friberg *et al*, 2006), which is in accordance with our findings, and baseline recreational physical activity appears to be more strongly associated with endometrial cancer risk than long-term recreational physical activity.

Importantly our study investigated the effects of different intensities of physical activity throughout a woman's life. Our findings for baseline strenuous activity are consistent with a recently reported pooled estimate of the association between endometrial cancer and physical activity from cohort studies published through 2006, which showed a 23% decreased risk of endometrial cancer for the most active compared with the least active women (OR = 0.77; CI, 0.70–0.85) (Voskuil *et al*, 2007).

Regarding moderate physical activity, several previous case–control (Littman *et al*, 2001; Matthews *et al*, 2005) and cohort (Terry *et al*, 1999; Schouten *et al*, 2004; Matthews *et al*, 2005) studies have demonstrated risk reductions for moderate physical activities. We found that long-term and baseline moderate physical activity was not significantly associated with endometrial cancer risk as, did Gierach *et al* (2009).

As obesity is a strong risk factor for endometrial cancer, we investigated whether BMI has a modifying effect on the inverse

Table 3. Adjusted[a] relative risks (RRs) and 95% confidence intervals (CIs) for the risk of incident invasive endometrial cancer associated with long-term and baseline recreational physical activity by body mass index (BMI) among 90 351 California Teachers Study women between 1995 and 2007

Category of physical activity	⩽0.50 (hours per week per year)		0.51-1.50 (hours per week per year)		1.51-2.99 (hours per week per year)		⩾3.00 (hours per week per year)			
BMI category	**Cases, *n***	**Referent**	**Cases, *n***	**RR (95% CI)**	**Cases, *n***	**RR (95% CI)**	**Cases, *n***	**RR (95% CI)**	**P_{trend}[b]**	**P-homogeneity**
Long-term physical activity by intensity										
Strenuous										
$<25\,kg\,m^{-2}$	167	1.00	98	0.91 (0.70–1.17)	84	0.96 (0.73–1.26)	87	0.96 (0.73–1.28)	0.82	
$\geqslant 25\,kg\,m^{-2}$	199	1.00	138	1.09 (0.87–1.35)	80	0.85 (0.65–1.11)	76	0.88 (0.66–1.18)	0.25	0.59
Moderate										
$<25\,kg\,m^{-2}$	102	1.00	112	1.07 (0.83–1.37)	110	1.07 (0.83–1.39)	112	0.93 (0.71–1.23)	0.42	
$\geqslant 25\,kg\,m^{-2}$	130	1.00	136	1.01 (0.80–1.27)	120	1.02 (0.79–1.31)	107	0.86 (0.66–1.13)	0.26	0.72
Baseline physical activity by intensity										
Strenuous										
$<25\,kg\,m^{-2}$	254	1.00	69	1.23 (0.94–1.61)	27	0.96 (0.64–1.44)	86	0.84 (0.65–1.08)	0.12	
$\geqslant 25\,kg\,m^{-2}$	370	1.00	53	0.79 (0.59–1.06)	30	1.11 (0.76–1.63)	40	0.61 (0.43–0.85)	0.006	0.20
Moderate										
$<25\,kg\,m^{-2}$	126	1.00	82	0.90 (0.69–1.18)	47	0.92 (0.67–1.28)	181	1.06 (0.86–1.31)	0.42	
$\geqslant 25\,kg\,m^{-2}$	208	1.00	116	1.10 (0.88–1.38)	47	1.01 (0.74–1.40)	122	0.98 (0.78–1.22)	0.85	0.34

[a]RRs are from multivariable Cox proportional hazards regression models using age (in days) as the time metric and stratified by age (in years) with the following variables included in each model: race, and BMI. Both, moderate physical activity and strenuous physical activity are fit simultaneously in a single model.
[b]Trends are fit to the median for each category.

association with physical activity. We observed stronger protective effects associated with higher levels of baseline strenuous physical activity among overweight and obese women, although we were unable to demonstrate statistically a modifying effect of BMI. Similarly, many cohort and case–control studies have not observed any effect modification by BMI as noted in recent reviews (Cust *et al*, 2007; Voskuil *et al*, 2007). Our findings are in contrast with one case–control study (Moradi *et al*, 2000) that observed a stronger effect in women with a lower BMI, but are consistent with several cohort (Furberg and Thune, 2003; Patel *et al*, 2008; Gierach *et al*, 2009) and case–control studies (Levi *et al*, 1993; Sturgeon *et al*, 1993) that found stronger associations with physical activity among women with a high BMI ($>25\,kg\,m^{-2}$). Physical activity may reduce endometrial cancer risk by maintaining energy balance and reducing excess adipose tissue (Cust *et al*, 2007). For very active individuals, BMI may be elevated because of muscle weight rather than as a representation of overweight or obesity, per se.

Physical activity may reduce endometrial cancer risk directly by decreasing levels of biologically available estrogens, as indicated by studies reporting lower oestrogen levels among more active women (Cauley *et al*, 1989; Madigan *et al*, 1998), or indirectly through lower body fat (McTiernan *et al*, 1998) resulting in reduced peripheral conversion of androgens to estrogens by aromatase occurring in adipose tissue (Siiteri, 1987). Vigorous and moderate-intensity exercise have been associated with improved insulin sensitivity, lower fasting insulin levels, increased levels of sex hormone-binding globulin and insulin-like growth factor binding protein-1 and a reduced prevalence of metabolic syndrome in women (Mayer-Davis *et al*, 1998; Irwin *et al*, 2000, 2002; Allen *et al*, 2003). Hyperinsulinaemia may affect endometrial cancer through various direct and indirect mechanisms, which may be altered with physical activity (Kaaks and Lukanova, 2002; Lukanova *et al*, 2004). Under those mechanisms, we would expect long-term physical activity to be most strongly associated with reduced endometrial cancer risk, thus our results are somewhat puzzling. However, baseline activity could have a more immediate effect thereby reducing the chances that existing hyperplasia progresses to endometrial cancer.

Strengths of this study include its prospective design, large number of incident endometrial cancer cases, and ability to identify and confirm cancer diagnoses through California's high-quality statewide cancer registry. As we used age as the time metric in our analyses, this ensured that women of the same age were compared with each other. We collected detailed measures of physical activity over multiple age periods, from high school to age 54 years and in the recent past. Thus, we were able to examine not only the effects of intensity of physical activity but also the timing and duration of activity on endometrial cancer risk. We were unable to differentiate between similar activities performed over a different number of days per week.

A potential limitation of our study is that we did not collect information on occupational or household physical activity. These additional sources of physical activity may be important contributors to total energy expenditure and may affect the association between physical activity and endometrial cancer (Moradi *et al*, 1998; John *et al*, 2010). A recent case–control study examined various sources of physical activity (recreation, transportation, chores and occupation activity) and found an inverse association with total, occupational and recreational physical activities (John *et al*, 2010). The CTA cohort consists of active and retired teachers, administrators and other public school professionals, and although we did not measure occupational activity, it is likely that most women who are active in the California public school system would have similar occupational activity levels, with the possible exception of physical education teachers. However, the length of time that the active teachers had been employed in the school system varies substantially, and we do not have information on other occupations held. We collected information on strenuous and moderate levels of physical activity by self-report, providing examples of activities at each level. Although it is possible that the reported levels may overestimate or underestimate actual activity, information was collected before endometrial cancer diagnosis and should not differ by disease status overall. Additionally, our measure for recent physical activity was not updated during follow-up; thus, how recent the variable is relative to endometrial cancer risk varies as duration of follow-up is extended. To address this, we did examine the association between recent physical activity and endometrial cancer during two time periods, 1995–2001 and 2002–2007, and the associations did not differ from that reported overall (data not shown). Further, due to the fact that we did not ask our participants to provide the exact forms of physical activity (i.e., running, walking, swimming, etc.) that they participated in, we were unable to calculate metabolic equivalent (MET) values and could not perform our analyses based on average MET values at varying stages of one's life. However, of importance, we examined the validity and reliability of our physical activity questionnaire. We found our questionnaire to be valid and reliable; however, these data are not yet published. We collected information on height and weight by self-report to calculate BMI; thus, it is possible that reported values may overestimate or underestimate actual height and weight. Nonetheless, information was collected before endometrial cancer diagnosis and should not differ by disease status.

In summary, these results add to the growing epidemiologic evidence that physical activity may be an important modifiable lifestyle factor affecting the risk of endometrial cancer. As few risk factors identified to date are potentially modifiable, the findings of this study are of particular public health relevance. Furthermore, women with higher body weight may have an added benefit from regular participation in physical activity as a means to reduce the risk of endometrial cancer. Of importance is to clarify the underlying mechanisms involved in the association between physical activity and endometrial cancer risk, particularly those relating to hormonal alterations.

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