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Original Contribution

Recreational Physical Activity and Sedentary Behavior in Relation to Ovarian Cancer Risk in a Large Cohort of US Women

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Factors that influence circulating sex hormones, such as physical activity, have been proposed to influence ovarian cancer risk; however, results from previous epidemiologic studies have been inconsistent. The authors examined the association among physical activity, sedentary behavior, and ovarian cancer risk in the American Cancer Society Cancer Prevention Study II Nutrition Cohort, a prospective study of cancer incidence and mortality, using information obtained at baseline in 1992. From 1992 to 2001, 314 incident ovarian cancer cases were identified among 59,695 postmenopausal women who were cancer free at enrollment. Cox proportional hazards modeling was used to compute hazard rate ratios while adjusting for potential confounders. No overall association was observed between measures of past physical activity or with recreational physical activity at baseline and risk of ovarian cancer in this study (for the highest category of physical activity compared with none: hazard rate ratio = 0.73, 95% confidence interval: 0.40, 1.34). However, a prolonged duration of sedentary behavior was associated with an increased risk (for $\geq$6 vs. $<$3 hours per day: hazard rate ratio = 1.55, 95% confidence interval: 1.08, 2.22; $p_{trend} = 0.01$). Results from this study suggest that high levels of sedentary behavior may increase the risk of ovarian cancer, but they do not support a major impact of light and moderate physical activity on ovarian cancer risk.

cohort studies; exercise; ovarian neoplasms

Abbreviations: CI, confidence interval; CPS-II, Cancer Prevention Study II; MET, metabolic equivalent; RR, hazard rate ratio.

Ovarian cancer is the seventh most common incident cancer and ranks fourth in terms of cancer deaths among US women (1). Age, nulliparity, and family history of breast and/or ovarian cancer are established risk factors for ovarian cancer (2–5). Additionally, oral contraceptive use has been shown to reduce risk of ovarian cancer (2–4, 6). Few other risk factors have been well established. Factors that potentially influence circulating sex hormones, such as physical activity, have been proposed as risk factors for ovarian cancer (7, 8).

To date, nine observational studies have examined the relation between physical activity and ovarian cancer risk with inconsistent results (9–17). Among case-control studies, three (9, 11, 15) of five (9, 11, 14, 15, 17) have reported that higher total physical activity is associated with lower ovarian cancer risk. In contrast, no association between total physical activity and ovarian cancer risk was reported in three prospective cohort studies (10, 12, 13), and a positive association between total physical activity and ovarian cancer risk was seen in the Iowa Women's Health Study (16).

Data concerning vigorous physical activity and ovarian cancer risk also are conflicting. Two studies that found no association with total physical activity suggested that vigorous activity was associated with lower ovarian cancer risk (12, 17); however, the positive association observed in the Iowa Women's Health Study strengthened when examining only vigorous physical activity, and results from the Nurses' Health Study suggested that increased risk was associated

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with vigorous physical activity (10). In one previous case-control study in China, Zhang et al. observed both lower ovarian cancer risk among physically active women (15) and higher risk associated with sedentary behavior (18). After adjustment for physical activity, they found an increased risk of ovarian cancer with high levels of sitting while at work, sitting while watching television, and total sitting duration (18). No other study has examined the association between hours sitting and risk of ovarian cancer.

We examined whether recreational physical activity or inactivity was associated with ovarian cancer risk among postmenopausal women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study in the United States.

MATERIALS AND METHODS

Study population

Women in this analysis were drawn from the 97,786 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality established by the American Cancer Society in 1992 as a subgroup of the larger 1982 CPS-II baseline mortality cohort (19). Most participants were aged 50–74 years at enrollment in 1992. At baseline, they completed a 10-page self-administered questionnaire that included questions on demographic, reproductive, medical, behavioral, environmental, and dietary factors. Beginning in 1997, follow-up questionnaires were sent to cohort members every 2 years to update exposure information and to ascertain newly diagnosed cancers. All follow-up questionnaire response rates (after multiple mailings) among living cohort members are at least 90 percent. The end of follow-up for the present analysis was August 31, 2001.

We excluded from this analysis 3,506 women who were lost to follow-up (i.e., they were alive at the time of the first follow-up questionnaire in 1997 but did not return the 1997 or any subsequent follow-up questionnaire), who reported prevalent cancer (except nonmelanoma skin cancer) at baseline ($n = 12{,}028$), who reported that they were not postmenopausal ($n = 4{,}269$), or who had a bilateral or unknown laterality oophorectomy at baseline ($n = 16{,}455$). We also excluded women with missing information on recreational physical activity at baseline ($n = 911$) or body mass index at baseline ($n = 906$). Finally, we also excluded reported cases of ovarian cancer that could not be verified through medical or cancer registry records ($n = 14$) or cases that were verified as nonepithelial ovarian cancer ($n = 2$). Women who did not return a 1999 or 2001 questionnaire were censored at the 1997 questionnaire date. Women also were censored at report of a bilateral oophorectomy on the 1997 or 1999 questionnaire. After all exclusions, the final analytical cohort consisted of 59,695 women with a mean age at study entry of 62.7 (standard deviation: 6.1) years.

Case ascertainment

This analysis included 314 verified incident cases of ovarian cancer diagnosed between the date of enrollment and August 31, 2001. Of these, 214 cases were identified initially by self-report on a follow-up questionnaire and subsequently verified from medical records ($n = 142$) or linkage with state cancer registries ($n = 72$). A previous study linking cohort participants with state cancer registries has shown that the Nutrition Cohort participants are highly accurate (93 percent sensitivity) in reporting any past cancer diagnoses (20). A total of 100 incident cases were identified as interval deaths (deaths that occurred between baseline in 1992 and the end of follow-up in 2001) through automated linkage of the entire cohort with the National Death Index (21). For most of these cases ($n = 93$), ovarian cancer was listed as the primary or a contributory cause of death (*International Classification of Diseases*, Ninth Revision, codes 183.0–183.9; Tenth Revision, codes C56.0–C56.9) (22, 23) during the interval between the date of enrollment and December 31, 2001. Additional information was obtained through linkage with state cancer registries for some of these ovarian cancer deaths ($n = 53$). For the remainder of interval deaths ($n = 7$), other reproductive or unspecified malignancies were listed as the primary or contributory cause of death, and additional information was obtained through linkage with state cancer registries to verify ovarian cancer diagnosis. We further identified ovarian cancer cases that were serous histologic subtype ($n = 165$) based on information from the medical or registry records. Sample size was insufficient to examine other histologic subtypes separately (mucinous ($n = 16$), endometrioid ($n = 25$), clear cell ($n = 13$), adenocarcinoma not otherwise specified ($n = 31$), other/not otherwise specified ($n = 24$)).

Measures of physical activity and sedentary behavior

Baseline recreational physical activity information was collected using the question: ''During the past year, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?'' Response to each activity included ''none,'' ''1–3 hours per week,'' ''4–6 hours per week,'' or ''7+ [≥7] hours per week.'' Summary metabolic equivalent (MET)-hours/week were calculated for each participant. A MET is the ratio of the metabolic rate during a specific activity to the resting metabolic rate (24). Because of the older age of this population, the summary MET score for each participant was calculated by multiplying the lowest number of hours within each category by the moderate-intensity MET score for each activity according to the *Compendium of Physical Activities* (24) to provide conservatively estimated summary measures. The MET scores for various activities were as follows (24): 3.5 for walking, 7.0 for jogging/running, 7.0 for lap swimming, 6.0 for tennis or racquetball, 4.0 for bicycling/stationary biking, 4.5 for aerobics/calisthenics, and 3.5 for dancing.

In addition to recreational leisure activity at baseline, nonrecreational leisure activity was also examined based on information collected from the question: ''During the past year, what was the average time per week you spent at the following kinds of activities: gardening/mowing/planting, heavy housework/vacuuming, heavy home repair/painting,

and shopping?'' The above algorithm was used to calculate MET-hours/week using the following values for each activity (24): 3.0 for gardening/mowing/planting, 2.5 for heavy housework/vacuuming, 3.0 for heavy home repair/painting, and 2.5 for shopping. Baseline nonrecreational leisure activity was categorized in quartiles of MET-hours/week as 0–5.0, >5.0–<10.0, 10.0–<18.5, or ≥18.5.

The baseline questionnaire also asked participants to recall physical activity at age 40 years using the question: ''At age 40, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?'' A summary MET score at age 40 years was created using the same method as described above. Recreational physical activity at baseline and age 40 years was categorized in MET-hours/week as none, >0–<8, 8–<17.5, 17.5–<31.5 or ≥31.5; 31.5 MET-hours/week corresponds to approximately 1 hour of moderate-paced walking (3.0 miles (4.8 km)/hour) per day. Another measure of past physical activity was obtained from a questionnaire completed in 1982, as participants in the CPS-II Nutrition Cohort had been enrolled previously in the larger CPS-II mortality study. The 1982 questionnaire asked for only a crude measure of physical activity: ''How much exercise do you get (work or play)?'' Possible responses were none, slight, moderate, or heavy. This measure of physical activity has been shown to correlate with all-cause mortality rates (25). Physical activity at age 40 years (as recalled in 1992) and activity reported in 1982 also were examined together with baseline 1992 exposure information to assess whether the risk of ovarian cancer was reduced among women who consistently reported being physically active.

Lastly, the baseline questionnaire asked participants: ''During the past year, on an average day, (not counting time spent at your job) how many hours per day did you spend sitting (watching TV [television], reading, etc.)?'' Responses included none, less than 3, 3–5, 6–8, and more than 8 hours per day. The duration of sedentary behavior at baseline was categorized as 0–<3, 3–5, ≥6, or missing hours/day.

Statistical analysis

We used Cox proportional hazards modeling (26) to calculate hazard rate ratios and corresponding 95 percent confidence intervals to examine the relation among measures of physical activity (recreational and nonrecreational), sedentary behavior, and ovarian cancer risk. Statistical Analysis System, version 9.1 (SAS Institute, Inc., Cary, North Carolina), software was used for all analyses. For each exposure variable, we assessed risk in two models, one adjusted only for age and the other adjusted for age, race, and other potential confounding factors. All Cox models were stratified on exact year of age at enrollment, and follow-up time in days was used as the time-axis. We tested the Cox proportional hazards assumption for all the factors included in the analysis and found no violations. Potential confounders included in the multivariate models were race (White, non-White), body mass index (weight (kg)/height (m)^2) (<25.0, 25.0–<30.0, ≥30.0), oral contraceptive use (never, <5 years, ≥5 years, ever use with unknown duration, missing), parity (nulliparous, 1–2, ≥3, missing), age in years at menopause (<45, 45–54, ≥55, unknown), age in years at menarche (<12, ≥12, missing), family history of breast and/or ovarian cancer (yes, no), simple hysterectomy (yes, no, missing), and postmenopausal hormone replacement therapy use (never, current estrogen-progestogen replacement therapy, current estrogen replacement therapy, former estrogen-progestogen replacement therapy, former estrogen replacement therapy, other, missing/unknown). We also examined the relation between these measures restricted to serous ovarian cancer tumors only.

Trend tests for baseline recreational and nonrecreational activity, physical activity at age 40 years, and duration of sedentary behavior were calculated by assigning the median value within each category to that category. Trend tests for physical activity in 1982 were obtained by using an ordinal variable corresponding with each level of physical activity. To test whether physical activity across multiple time points was associated with ovarian cancer risk, we combined baseline recreational physical activity with physical activity in 1982 (for consistency in the 10 years prior to baseline) and baseline physical activity with activity at age 40 years. To test whether any of the potential confounders described above modified the association between the main effects measures and ovarian cancer risk, we examined each factor in a separate model by constructing multiplicative interaction terms with each risk factor and comparing the interaction model with the base model without the interaction terms. Because of small numbers in some strata, categories of potential effect modifiers were sometimes collapsed. Statistical interaction was assessed in multivariate models using the likelihood ratio test, and $p < 0.05$ was considered statistically significant (27).

RESULTS

Approximately 9 percent ($n = 5{,}433$) of the women reported no recreational physical activity at baseline (table 1). Among physically active women (defined as those reporting any recreational physical activity at baseline), the median MET expenditure was 8.0 MET-hours/week, corresponding to approximately 2 hours of moderately paced walking per week. Physically active women, regardless of level of MET expenditure, engaged primarily in activities judged to be of lower intensity (walking, biking, aerobics/calisthenics, or dancing) rather than of moderate or higher intensity (jogging/running, swimming, or tennis/racquetball). Physically active women were more likely to be lean and to have ever used oral contraceptives. Physically active women at baseline also were more likely to have been physically active in 1982 and at age 40 years, and they were more likely to engage in nonrecreational activity at baseline (table 1).

No overall association was observed between the level of recreational physical activity at baseline and the overall risk of ovarian cancer (table 2). Women in the highest category of recreational physical activity (≥31.5 MET-hours/week) had 27 percent lower risk of ovarian cancer (hazard rate ratio (RR) = 0.73, 95 percent confidence interval (CI): 0.40, 1.34)

TABLE 1. Selected study participant characteristics* in relation to recreational physical activity at baseline among 59,695 women in the Cancer Prevention Study II Nutrition Cohort, 1992–2001

Variable	Physical activity MET† in 1992 (total: $n = 59,695$)				
	None ($n = 5,433$)	>0–<8 ($n = 24,297$)	8–<17.5 ($n = 14,597$)	17.5–<31.5 ($n = 11,331$)	≥31.5 ($n = 4,037$)
Median recreational activity MET-hours/week	0	3.5	14.0	24.0	39.5
Moderate/high-intensity activities‡ (%)	0.0	1.7	9.8	8.6	34.4
Median nonrecreational MET-hours/week	8.0	8.0	8.0	12.5	13.0
Median MET-hours/week at age 40 years	3.5	7.0	11.0	18.0	28.5
% with moderate or high exercise in 1982	56.9	67.1	75.5	81.7	88.1
Median hours/day spent sedentary	4	4	4	4	2
Body mass index, kg/m^2 (mean (SE†))*	26.9 (0.06)	25.9 (0.03)	25.0 (0.04)	24.7 (0.04)	24.1 (0.07)
Age at menopause, years (mean (SE))*	48.5 (0.11)	48.8 (0.05)	49.1 (0.07)	49.0 (0.08)	49.1 (0.13)
Age at menarche, years (mean (SE))*	12.7 (0.02)	12.7 (0.01)	12.7 (0.01)	12.8 (0.01)	12.8 (0.02)
Race (% White)*	97.0	97.4	97.5	97.4	97.5
Parity (%)*					
0	7.4	7.4	6.8	6.9	6.8
1	7.8	7.3	6.4	6.9	6.4
2–3	51.3	52.1	53.6	53.3	54.0
≥4	31.3	31.6	31.3	30.9	30.9
Missing	2.2	1.7	1.9	2.0	1.8
Oral contraceptive use (%)*					
Missing	1.7	1.3	1.1	1.2	0.9
Never use	64.1	62.4	60.7	62.8	60.2
Ever use/years unknown	1.6	1.4	1.4	1.4	1.4
<5 years	17.9	18.9	20.0	18.9	20.3
≥5 years	14.6	16.0	16.9	15.6	17.0
Family history of breast and/or ovarian cancer (%)*					
Yes	20.9	21.4	20.4	21.4	22.9

* Values are standardized to the age distribution of the study population.
† MET, metabolic equivalent; SE, standard error.
‡ Low-intensity activities are defined as those with MET scores of ≤4.5 (walking, biking, aerobics/calisthenics, or dancing), and moderate/high-intensity activities are defined as those with MET scores of >4.5 (jogging/running, swimming, or tennis/racquetball).

than did women who reported no physical activity at baseline (table 2). However, the test for trend was not statistically significant whether we included ($p_{trend} = 0.95$) or excluded ($p_{trend} = 0.81$) women who reported no recreational physical activity. Similarly, no association was observed when examining levels of moderate- and/or high-intensity physical activity (jogging/running, swimming, tennis/racquetball) separately and ovarian cancer risk. The risk among women who engaged in only low-intensity activities was the same as among women who reported no recreational physical activity (low only: RR = 0.95, 95 percent CI: 0.64, 1.39); however, the risk was slightly lower among women who reported any moderate- or higher-intensity activities compared with the risk among women reporting no physical activity (RR = 0.78, 95 percent CI: 0.47, 1.29).

We also examined the relation between nonrecreational activity at baseline and ovarian cancer risk (table 2). The risk of ovarian cancer was not associated with the sum of such activities as gardening, shopping, and housework (for ≥18.0 MET-hours/week vs. 0–5 MET-hours/week: RR = 1.07, 95 percent CI: 0.79, 1.46; $p_{trend} = 0.56$). We also examined whether total physical activity at baseline (recreational plus nonrecreational activity) was associated with ovarian cancer risk; the association was very similar to that for recreational physical activity alone (data not shown). Additionally, we examined the association of ovarian cancer risk with physical activity at age 40 years and with exercise levels reported in 1982 (table 2). Neither physical activity at age 40 years (for ≥31.5 METs vs. none: RR = 1.09, 95 percent CI: 0.68, 1.74; $p_{trend} = 0.58$) nor exercise reported in 1982 (for heavy vs. no/slight exercise: RR = 0.88, 95 percent CI: 0.49, 1.55; $p_{trend} = 0.83$) was associated with the risk of ovarian cancer. Furthermore, being physically active across multiple time points was not associated with the risk of total ovarian cancer (data not shown).

Since sedentary behavior and physical activity at baseline were not correlated strongly in the cohort ($r = -0.05$), we examined sedentary behavior as an alternate measure of

TABLE 2. Hazard rate ratios and 95% confidence intervals for measures of recreational physical activity (and inactivity) at various points in time and ovarian cancer, Cancer Prevention Study II Nutrition Cohort, 1992–2001

	No. of cases/ population	Person-years	Age-adjusted hazard rate ratio	95% confidence interval	Multivariable-adjusted hazard rate ratio*	95% confidence interval
Baseline recreational activity MET†-hours/week						
None	29/5,433	42,013	1.00	Referent	1.00	Referent
>0–<8	117/24,297	192,996	0.88	0.58, 1.32	0.87	0.58, 1.30
8–<17.5	83/14,597	116,521	1.02	0.67, 1.55	1.00	0.65, 1.52
17.5–<31.5	68/11,331	90,466	1.07	0.69, 1.66	1.03	0.67, 1.60
≥31.5	17/4,037	32,360	0.76	0.42, 1.38	0.73	0.40, 1.34
					$p_{trend} = 0.95$	
Baseline nonrecreational activity MET-hours/week						
0–5.0	78/15,650	123,274	1.00	Referent	1.00	Referent
>5.0–<10.0	68/13,939	111,382	0.96	0.69, 1.33	0.96	0.70, 1.33
10.0–<18.5	81/14,416	115,018	1.09	0.80, 1.49	1.08	0.79, 1.48
≥18.5	82/15,039	119,680	1.07	0.79, 1.46	1.07	0.79, 1.46
Missing	5/651	5,003	1.47	0.59, 3.63	1.40	0.57, 3.47
					$p_{trend} = 0.56$	
MET-hours/week at age 40 years						
None	39/8,659	69,082	1.00	Referent	1.00	Referent
>0–<8	120/19,777	157,678	1.34	0.93, 1.92	1.34	0.93, 1.92
8–<17.5	58/12,189	97,248	1.06	0.71, 1.59	1.06	0.71, 1.59
17.5–<31.5	61/11,440	90,067	1.17	0.78, 1.75	1.17	0.78, 1.75
≥31.5	32/6,588	52,173	1.09	0.68, 1.74	1.09	0.68, 1.74
Missing	4/1,042	8,109	0.78	0.28, 2.19	0.76	0.27, 2.12
					$p_{trend} = 0.58$	
Exercise in 1982						
None/slight	75/15,738	125,196	1.00	Referent	1.00	Referent
Moderate	222/40,021	317,903	1.12	0.86, 1.45	1.11	0.85, 1.45
Heavy	14/3,198	25,358	0.89	0.50, 1.58	0.88	0.49, 1.55
Missing	3/738	5,900	0.81	0.26, 2.56	0.77	0.24, 2.46
					$p_{trend} = 0.83$	
Baseline sitting (hours/day)						
<3	124/27,493	221,109	1.00	Referent	1.00	Referent
3–5	141/24,967	197,559	1.19	0.93, 1.52	1.21	0.95, 1.54
≥6	41/5,781	44,385	1.51	1.06, 2.15	1.55	1.08, 2.22
Missing	8/1,454	11,303	1.19	0.58, 2.42	1.15	0.56, 2.36
					$p_{trend} = 0.01$	

* Adjusted for age, race, body mass index, family history of breast and/or ovarian cancer, age at menopause, age at menarche, oral contraceptive use, parity, hysterectomy, and postmenopausal hormone replacement therapy use.

† MET, metabolic equivalent.

physical activity (or inactivity) in this relatively homogeneous population. Furthermore, duration of sedentary behavior during leisure time better predicted for weight gain prospectively during follow-up than did recreational physical activity; thus, sedentary behavior may measure physical activity more accurately in this cohort. Thus, we also examined the association between ovarian cancer risk and sedentary behavior at baseline (table 2). Women who spent more time sedentary watching television, reading, and so on had a 55 percent higher risk of developing ovarian cancer than did women with low levels of sedentary behavior (<3 hours/day) (RR = 1.55, 95 percent CI: 1.08, 2.22; $p_{trend} = 0.01$). Additionally, there was no appreciable change in risk estimates when simultaneously adjusting for recreational

physical activity and sedentary behavior in multivariate models (data not shown).

The association between physical activity or inactivity and ovarian cancer did not differ when examining serous ovarian cancer tumors independently. We did not observe a significant inverse association ($p_{trend} = 0.61$) between physical activity at baseline and risk of serous ovarian tumors (data not shown). The relative risk for serous ovarian cancer tumors was marginally higher than the overall estimates among women who were most sedentary (≥6 hours/day) compared with women who reported less sedentary behavior (<3 hours/day) at baseline (RR = 2.13, 95 percent CI: 1.34, 3.38). The associations were not stronger for serous tumors than for all histologic types combined in relation to nonrecreational physical activity, physical activity at age 40 years, or exercise reported in 1982 (data not shown).

We also tested for potential effect modification but found no suggestion of interactions between main effects measures of physical activity or sedentary behavior and any of the other potential risk factors included in this analysis (data not shown). Finally, we examined the combined effects of baseline recreational physical activity and sedentary behavior in relation to ovarian cancer risk, but risk estimates in women who had both low levels of physical activity and more sedentary behavior (<8 MET-hours/week and ≥6 hours/day sitting) did not differ from risk estimates for sedentary behavior alone (data not shown). In a sensitivity analysis, we changed the time-axis in all Cox models to age and observed no differences in risk estimates (data not shown).

DISCUSSION

Results from this prospective study do not support a major role of light and moderate physical activity (recreational or nonrecreational) on the risk of ovarian cancer in postmenopausal women. The risk of ovarian cancer also was not associated with measures of physical activity at different periods in time (1982 or age 40 years) or with physical activity measured across multiple time points. In contrast, results from this study do support an association between duration of sedentary behavior and ovarian cancer risk. Women who spent 6 or more hours per day sedentary while watching television, reading, and so on had 55 percent higher incidence of ovarian cancer than did women who engaged in less sedentary behavior (<3 hours/day), even after adjustment for recreational physical activity.

These results are consistent with five (10, 12–14, 17) of nine (9–17) previous studies that observed no overall association between total recreational physical activity and ovarian cancer risk. Physical activity, however, was associated with increased risk of ovarian cancer in one prospective study of female farmers in the United States (16) and with decreased risk in three other studies (9, 11, 15). None of these three studies included lower-intensity activities in their physical activity assessment; in addition, two of them were conducted in Australia (11) and China (15), where activity patterns may differ from those in the United States. The only previous study that has looked at sedentary behavior was a case-control study conducted in China, which found that a higher total sitting duration was associated with increased risk (for ≥10 vs. <4 hours/day: odds ratio = 1.77, 95 percent CI: 1.0, 3.1; $p_{trend} = 0.08$) (18).

Our analyses relating risk to higher-intensity physical activity were limited by the small number of cases reporting these activities and are not inconsistent with the hypothesis that moderate- or higher-intensity activities may be associated with lower risk of ovarian cancer. Two US studies reported lower risk of postmenopausal ovarian cancer among women engaging in vigorous physical activity (12, 17); however, the positive association between physical activity and risk of ovarian cancer observed in the Iowa Women's Health Study strengthened when examining only vigorous physical activity (16). Vigorous activity also was associated with higher risk of ovarian cancer in the Nurses' Health Study, although no association was seen with total physical activity. However, the analysis of nurses was based on a population of mostly premenopausal women aged 30–55 years whose level of physical activity may be higher than that of the women in our study and whose physical activity may not have been sufficient to disrupt ovulation, but rather to shorten ovulatory cycles and slightly increase risk (10).

Various endogenous hormones have been hypothesized to be important in ovarian carcinogensis. Exposures to estrogens, androgens, and gonadotropins have been proposed to increase ovarian epithelial cell proliferation, whereas exposure to progesterone has been suggested to decrease stimulation of ovarian epithelial cells (8, 28). Physical activity has been shown to decrease postmenopausal estrogen levels directly or indirectly through reduced peripheral fat stores, the major source of postmenopausal estrogen production (29–32). In other studies, sedentary behavior has been associated with obesity and with metabolic abnormalities, resulting in increased circulating estrogen, insulin, and other hormones that may promote cell proliferation (33–37). On the other hand, physical activity has been associated with increased pituitary gonadotropins (through part of a negative-feedback relation with estrogen) and androgens, as well as decreased progesterone, that could infer an increased risk of ovarian cancer (8). Since physical activity has been shown to affect these various hormones differently, it is unclear how physical activity may influence ovarian cancer risk.

Our study has several limitations. We had no individual information on the intensity of each behavior, increasing the likelihood of misclassification of true energy expenditure. Although the physical activity questions that we used have not been validated and are subject to misreporting, they are very similar to those used and validated in another prospective study. That study found strong correlations between the activity reported on past-week activity recalls and 7-day diaries and that reported on the questionnaire ($r = 0.79$ and 0.62, respectively) (38). Furthermore, we do not believe that the limitations in our measures of physical activity entirely explain the lack of association observed, as physical activity has been associated with a lower risk of breast and colon cancer in this cohort (39, 40).

Another limitation was our inability to adequately examine higher-intensity activities, since most highly active women engaged in walking with the addition of modest

amounts of the other six reportable activities (thus limiting the power to examine such a relation). Furthermore, we were unable to examine whether vigorous physical activity for short periods of time will lower ovarian cancer risk, irrespective of the time spent in sedentary behavior. The amount of time that women in Westernized countries spend in sedentary behavior is increasing, and most physical activity is voluntary (e.g., going to the gym, running); however, because of the age distribution of the women in this study and the relatively few women in our study who reported vigorous activity, we were unable to answer this important question. Finally, we were limited in our ability to examine all histologic subtypes of epithelial ovarian cancer.

The strengths of this study include the prospective design that reduced the likelihood of differential reporting of recalled exposure information and eliminated the possibility of recall bias. In addition, we also had the ability to test for potential confounding by the most important ovarian cancer risk factors. Finally, while the relatively homogeneous nature of the women in this study reduced the range of the physical activity exposure variables, it also reduced the likelihood of residual confounding.

In summary, light and moderate levels of physical activity are not significantly associated with ovarian cancer risk in this prospective study. It remains unclear whether higher-intensity physical activity is associated with ovarian cancer risk. However, results from this study suggest that sedentary behavior is associated with increased ovarian cancer risk. Thus, public health recommendations should focus on reducing sedentary behavior in addition to increasing physical activity. Further research is needed to clarify the association between physical activity and ovarian cancer risk, with a focus in observational studies on better understanding the etiologic role of endogenous hormones in ovarian carcinogenesis.

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