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The role of body weight in the relationship between physical activity and endometrial cancer: Results from a large cohort of US women

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Factors influencing circulating estrogen levels, insulin-mediated pathways or energy balance through obesity-related mechanisms, such as physical activity, have been proposed as potential risk factors for endometrial cancer. We examined measures of physical activity in relation to endometrial 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 2003, 466 incident endometrial cancers were identified among 42,672 postmenopausal women with intact uteri who were cancer-free at enrollment. Cox proportional hazards modeling was used to compute hazard rate ratios (RR) while adjusting for potential confounders. To assess the role of body mass index (BMI) in this relationship, we computed multivariate RR with and without adjustment for BMI and stratifying by BMI. All measures of physical activity and the avoidance of sedentary behavior were associated with lower endometrial cancer risk. Baseline recreational physical activity was associated with 33% lower risk (RR = 0.67, 95% CI 0.44–1.03 for 31.5+ *vs.* <7 MET-hr/week, trend $p = 0.007$) in the multivariate model without BMI. However, the trend was attenuated after further adjustment for BMI (trend $p = 0.18$). BMI significantly modified the association between physical activity and endometrial cancer risk (heterogeneity of trends $p = 0.01$). The inverse relationship was seen only among overweight or obese women (trend $p = 0.003$) and not in normal weight women (trend $p = 0.51$). In summary, light and moderate physical activity including daily life activities were associated with lower endometrial cancer risk in our study, especially among women who are overweight or obese.

Key words: physical activity; exercise; sedentary behavior; endometrial cancer; prospective cohort

Endometrial cancer is the fourth most common incident cancer among US women.[1] Important risk factors for endometrial cancer include obesity, postmenopausal unopposed estrogen use and nulliparity.[2] Type II diabetes has also been associated with increased risk.[3] Few other risk factors for endometrial cancer have been well-established. Physical activity has been proposed to protect against endometrial cancer. Physical activity influences circulating estrogen levels and insulin-mediated pathways both through its effects on energy balance and adiposity and directly through independent pathways.[4–6]

To date, 17 observational studies have examined the relationship between recreational (leisure-time) physical activity and endometrial cancer risk (reviewed in Refs. 7–10). Although only half of these studies reached statistical significance in their findings,[9–16] the majority suggest a benefit with regular physical activity in lowering endometrial cancer risk. A recent meta-analysis[8] provided summary risk estimates of a 27% decreased risk of endometrial cancer from case-control studies (95% CI, 0.62–0.86) and a 23% decreased risk from cohort studies (95% CI, 0.70–0.85) when comparing the most active women with the least active women.

Researchers have also examined the association between endometrial cancer and nonrecreational activities in daily life, such as household chores, shopping and gardening. These activities are usually less intense than the recreational activities generally recommended for chronic disease prevention, but are as or more commonly done. Whether these activities have any potential health benefits is unknown. Five previous studies (reviewed in Ref. 7) have examined the role of these household activities; 4 of these reported a significant inverse relationship between the highest levels of household activity and risk of endometrial cancer.[9,11,17,18] Two other studies reported an increased risk of endometrial cancer in sedentary women.[11,19]

Another important unresolved question is whether body weight confounds, modifies or is an intermediary in the relationship between physical activity and endometrial cancer risk. Most previous studies have adjusted for measures of body mass in multivariate models (reviewed in Ref. 8). Body mass index (BMI) attenuates the relationship between physical activity and risk when added to multivariate models. Eleven previous studies also examined whether body weight is an effect modifier of the relationship between physical activity and endometrial cancer.[9,11,12,15,17–23] Most of these studies found no statistical interaction between BMI and physical activity on the multiplicative scale; however, 3 studies reported significantly lower relative risk estimates associated with regular physical activity among overweight or obese women than normal weight women.[17,18,21]

To further clarify the relationship between physical activity and risk of endometrial cancer, we examined whether recreational physical activity, nonrecreational household activities or sedentary behavior was associated with endometrial cancer risk, and whether these associations differed by body weight among postmenopausal women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study in the US.

Material 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.[24] 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 88%. End of follow-up for the present analysis was June 30, 2003.

We excluded from this analysis 3,190 women who were lost to follow-up (*i.e.*, alive at 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 ($N = 12,053$), who reported not being postmenopausal ($N = 4,291$) or who had a hysterectomy or unknown hysterectomy status at baseline ($N = 30,724$). We also excluded women with missing information on recreational physical activity

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at baseline (N = 640) or BMI at baseline (N = 756). To eliminate the strong effect of estrogen-only hormone replacement therapy (ERT) on endometrial cancer and the possibility that reports of ERT only use were in error (because this regimen is contraindicated in women with an intact uterus), we excluded women who reported current ERT use in 1992 (N = 1,583) and those with current or past postmenopausal hormone use of unknown type in 1992 (n = 1,812). Finally, we excluded reported cases of endometrial cancer that could not be verified through medical or cancer registry records (N = 33) or cases with missing or potentially unrelated histologies such as endometrial stromal sarcoma (histology code 8930), adenosarcoma (code 8933), Mullerian mixed tumor (code 8950), endometrial adenofibroma (code 8381) and carcinosarcoma (code 8980) (n = 32). The etiology of these less common tumors is thought to be different from endometrial carcinomas. Women who did not return a 1999, 2001 or 2003 questionnaire were censored at the return of their last questionnaire. Women who underwent a hysterectomy were censored when first reported on the 1997, 1999 or 2001 questionnaire. After all exclusions, the final analytic cohort consisted of 42,672 women with a mean age of 62.8 (± 6.0 SD) years when enrolled in the study.

Case ascertainment

This analysis included 466 verified incident cases of endometrial cancer diagnosed between the date of enrollment and June 30, 2003. Of these, 433 cases were identified initially by self-report on a follow-up questionnaire and subsequently verified from medical records (n = 326) or linkage with state cancer registries (n = 107). A previous study linking cohort participants with state cancer registries has shown that the Nutrition Cohort participants are highly accurate (93% sensitivity) in reporting any past cancer diagnoses.[25] An additional 9 cases were reported by participants as another type of cancer, but were found to be endometrial cancer upon examination of registry records. Lastly, 24 incident cases were initially identified as interval deaths (deaths that occurred between baseline in 1992 and the end of follow-up in 2003) through automated linkage of the entire cohort with the National Death Index,[26] and subsequently verified through linkage with state cancer registries.

Measures of physical activity and sedentary behavior

Baseline information on recreational physical activity 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 hr per week," "4–6 hr per week" or "7+ hr per week." Summary MET-hr/week were calculated for each participant. A MET, or metabolic equivalent, is the ratio of metabolic rate during a specific activity to resting metabolic rate.[27] 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 times the moderate intensity MET score for each activity according to the Compendium of Physical Activities[27] to provide conservatively estimated summary measures. The MET scores for various activities were[27]: 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. Recreational physical activity at baseline was categorized in MET-hr/week as none, >0–<7, 7–<17.5, 17.5–<31.5 or ≥31.5. For reference, 31.5 MET-hr/week corresponds to approximately 1 hr of moderate-paced walking (3.0 mph) per day.

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-hr/week using the following values for each activity[27]: 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-hr/week as none, >0–5.0, >5.0–<10.0, 10.0–<18.5 or ≥18.5.

For both recreational and nonrecreational physical activity, women who reported being inactive were not used as the referent group because of the possibility that their complete inactivity may be due to underlying conditions related in some way to endometrial cancer risk. If inactive women suffer from other health conditions that are hormone-related and impair their ability to engage in physical activity (such as severe osteoporosis), the association between inactivity and endometrial cancer risk may be confounded.

We assessed sedentary behavior based on the question "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, reading, etc.)?" Responses included "none, less than 3, 3–5, 6–8, more than 8 hr per day." Sedentary behavior at baseline was categorized as 0–<3, 3–5, ≥6 or missing hr/day.

The baseline questionnaire also asked participants to recall physical activity at age 40 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 was created using the same method for baseline recreational activity described above. Recreational physical activity at age 40 was categorized in MET-hr/week as none, >0–<7, 7–<17.5, 17.5–<31.5, 31.5–<42.0 or ≥42.0. Another measure of past physical activity was obtained from a questionnaire completed in 1982 when participants in the CPS-II Nutrition Cohort were enrolled in the larger CPS-II mortality study. The 1982 questionnaire asked "How much exercise do you get (work or play)?" with possible responses: "none, slight, moderate or heavy." Although crude, this measure of physical activity has been shown to correlate with all-cause mortality rates.[28] The self-reported activity level in 1982 was combined with the more detailed information on 1992 recreational physical activity to examine whether risk of endometrial cancer was reduced among women who consistently reported being physically active in both 1982 and 1992. Women who reported being "none or slight" in 1982 and <17.5 MET-hr/week in 1992 were categorized as "consistently low," those reporting "moderate or heavy" in 1982 and 17.5+ MET-hr/week in 1992 were categorized as "consistently high," those reporting "none or slight" in 1982 and 17.5+ MET-hr/week in 1992 were categorized as "increasing low to high" and those reporting "moderate or heavy" in 1982 and <17.5 MET-hr/week in 1992 were classified as "decreasing high to low."

Statistical analysis

We used Cox proportional hazards modeling[29] to calculate hazards rate ratios (RR) and corresponding 95% confidence intervals (CI) to examine the relationship between measures of physical activity (recreational and nonrecreational), sedentary behavior and endometrial cancer risk. Statistical Analysis Software (SAS), v 9.1 was used for all analyses. For each exposure variable, we assessed risk in 3 models, one adjusted only for age, the second adjusted for age and other potential confounding factors except BMI and the third adjusting for all potential confounding factors including BMI. 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 each exposure measure and found no violations. Potential confounders included in the multivariate models were BMI [weight (kg)/height (m^2)] (<25.0, 25.0–<27.5, 27.5–<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 at men-

TABLE I – SELECTED STUDY PARTICIPANT CHARACTERISTICS[1] IN RELATION TO RECREATIONAL PHYSICAL ACTIVITY AT BASELINE AMONG 42,672 WOMEN IN THE CPS-II NUTRITION COHORT, 1992–2001

Variable	Baseline recreational activity MET-hr/week (total n = 42,672)				
	None (n = 3,854)	0–<7 (n = 13,445)	7–<17.5 (n = 14,365)	17.5–<31.5 (n = 8,112)	31.5+ (n = 2,896)
Median recreational activity MET-hr/week	0	3.5	11.5	24.0	39.5
Median nonrecreational MET-hr/week	8.0	8.0	8.0	12.5	13.0
Median recreational MET-hr/week, age 40	3.5	3.5	9.5	18.0	28.5
Moderate or high exercise in 1982 (%)	56.9	65.8	73.6	81.5	88.4
Median hr/day spent sedentary	4.0	4.0	4.0	4.0	1.5
BMI[1] (mean ± SE)	26.9 ± 0.08	25.9 ± 0.04	25.2 ± 0.04	24.7 ± 0.05	24.1 ± 0.09
Age at menopause[1] (mean ± SE)	50.0 ± 0.09	50.4 ± 0.05	50.5 ± 0.04	50.5 ± 0.06	50.6 ± 0.10
Age at menarche[1] (mean ± SE)	12.8 ± 0.02	12.8 ± 0.01	12.8 ± 0.01	12.8 ± 0.02	12.8 ± 0.03
Estimated kcal/day[1] (SE)	1,374 (7.9)	1,358 (4.2)	1,353 (4.1)	1,370 (5.4)	1,411 (9.0)
Race[1] (% White)	97.2	97.8	97.8	97.7	97.7
Parity[1] (%)					
0	8.5	8.0	7.7	7.6	7.3
1–2	34.1	32.7	32.5	33.5	32.5
3+	55.1	57.5	57.9	56.8	58.2
Missing	2.2	1.8	1.8	2.1	1.9
Oral contraceptive use[1] (%)					
Never use	65.6	64.2	62.2	64.0	61.4
<5 years	17.0	17.7	18.7	17.8	19.0
5+ years	14.0	15.6	16.7	15.8	17.5
Ever use/years unknown	1.7	1.3	1.2	1.2	1.2
Missing	1.6	1.2	1.1	1.1	0.9
Ever use of HT[1] (%)	36.3	41.3	43.2	42.2	43.4
Ever smoked[1]	50.1	42.6	44.6	46.2	51.9
History of diabetes[1] (%)	7.6	5.9	5.3	5.1	4.6

[1]Values are standardized to the age distribution of the study population.

opause (<45, 45–49, 50–54, 55+, unknown), age at menarche (<12, 12+, missing), postmenopausal hormone therapy use (HT) (never, current, former, other, missing/unknown), personal history of diabetes (yes, no), smoking status (never, current, former, ever unknown status, missing) and total energy intake (in quartiles). HT use and history of diabetes were modeled as time-varying covariates using information obtained in 1992, 1997, 1999 and 2001.

Trend tests for baseline recreational and nonrecreational activity, physical activity at age 40 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 to each level of physical activity. To test whether physical activity across multiple time points was associated with endometrial cancer risk, we combined baseline recreational physical activity with physical activity in 1982 as an index of consistency in the 10-years prior to baseline. To test whether any of the potential confounders described above modified the association between the main effect measures and endometrial cancer risk, we examined each factor in a separate model by constructing multiplicative interaction terms with each risk factor and comparing the interaction model to the base model without the interaction terms. Because of small numbers in some strata, categories of potential effect modifiers were sometimes combined. Statistical interaction was assessed in multivariate models using the likelihood ratio test and a p-value <0.05 was considered statistically significant.[30]

Results

Approximately 9% (n = 3,854) of women reported no recreational physical activity at baseline (Table I). Among physically active women (defined as those reporting any recreational physical activity at baseline), the median MET expenditure was 8.0 MET-hr/week, corresponding to approximately 2 hr of moderately paced walking per week. Physically active women, regardless of level of energy expenditure, engaged primarily in activities judged to be of low to moderate intensity (walking, biking, aerobics or dancing) rather than higher intensity (jogging/running, swimming, tennis/racquetball). Physically active women were more likely to be lean and have ever used oral contraceptives and postmenopausal HT. Physically active women were also more likely to have been physically active in the past (both as measured in 1982 and recalled from age 40) and to engage in various household (nonrecreational) activities (Table I).

Every measure of baseline physical activity and the avoidance of sedentary behavior were associated with lower endometrial cancer risk (Table II). Recreational physical activity at baseline was associated with a 33% lower risk (RR = 0.67, 95% CI 0.44–1.03 for 31.5+ *vs.* <7 MET-hr/week, trend p = 0.007) in the multivariate model without adjustment for BMI (Table II). However, the association was attenuated when BMI was added to the model (RR = 0.79, 95% CI 0.52–1.22 for 31.5+ *vs.* <7 MET-hr/week, trend p = 0.18). Similarly, baseline household activity was marginally associated with lower endometrial cancer risk (RR = 0.79, 95% CI, 0.61–1.03 for >18.5 MET-hr/week *vs.* >0–<5 MET-hr/week; trend p = 0.07); further adjustment for BMI only slightly attenuated this association (Table II). Finally, adjustment for BMI greatly influenced the relationship between endometrial cancer and sedentary behavior at baseline (6+ *vs.* <3 hr/day sitting RR = 1.40, 95% CI 1.03–1.89 without adjustment for BMI *versus* RR = 1.18, 95% CI 0.87–1.59 with adjustment for BMI).

With regard to past measures of physical activity, prospectively reported exercise in 1982 showed a similar reduction in risk of endometrial cancer as baseline recreational physical activity, before adjusting for BMI (RR = 0.67, 95% CI 0.42–1.07 heavy *vs.* none/slight). Recreational physical activity at age 40 (as recalled in 1992) was not associated with endometrial cancer risk (Table II). There were no appreciable changes in any risk estimates when simultaneously adjusting for recreational physical activity, nonrecreational activity or sedentary behavior in multivariate models (data not shown). Consistently high levels of physical activity over the 10-years prior to baseline (1982 and 1992) were associated with lower risk of endometrial cancer even after adjustment for BMI (RR = 0.75, 95% CI, 0.56–0.99 for consistently high *vs.* consistently low activity levels) (Table II).

When we tested for potential effect modification by other endometrial cancer risk factors, we found evidence of effect modification by BMI (heterogeneity of trends p = 0.01). In normal weight women (BMI < 25.0), we observed no association between rec-

TABLE II – HAZARD RATE RATIOS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR MEASURES OF PHYSICAL ACTIVITY AT VARIOUS POINTS IN TIME AND ENDOMETRIAL CANCER, CPS-II NUTRITION COHORT, 1992–2001

	Cases	*p*-years	RR[1] (95% CI)	RR[2] (95% CI)	RR[3] (95% CI)
Baseline recreational activity MET-hr/week					
None	43	34,622	0.92 (0.66–1.28)	0.93 (0.67–1.30)	0.84 (0.60–1.17)
0<–<7	170	124,302	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
7–<17.5	157	133,553	0.86 (0.69–1.07)	0.86 (0.70–1.07)	0.92 (0.74–1.14)
17.5–<31.5	72	75,456	0.70 (0.53–0.92)	0.70 (0.53–0.93)	0.80 (0.60–1.05)
31.5+	24	27,264	0.65 (0.42–1.00)	0.67 (0.44–1.03)	0.79 (0.52–1.22)
				p-trend = 0.007	*p*-trend = 0.18
Baseline nonrecreational activity MET-hr/week[4]					
None	11	5,473	1.45 (0.78–2.69)	1.44 (0.78–2.66)	1.31 (0.71–2.44)
>0–5.0	132	96,620	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>5.0–<10.0	110	93,290	0.87 (0.67–1.11)	0.87 (0.67–1.12)	0.91 (0.70–1.17)
10.0–<18.5	103	96,592	0.77 (0.60–1.00)	0.77 (0.60–1.00)	0.79 (0.61–1.02)
18.5+	106	99,250	0.78 (0.60–1.01)	0.79 (0.61–1.03)	0.83 (0.64–1.07)
				p-trend = 0.07	*p*-trend = 0.13
Baseline sitting[4] (hr/day)					
<3	195	184,173	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
3–5	203	165,561	1.13 (0.93–1.38)	1.13 (0.92–1.38)	1.02 (0.83–1.25)
6+	56	36,584	1.40 (1.04–1.89)	1.40 (1.03–1.89)	1.18 (0.87–1.59)
				p-trend = 0.05	*p*-trend = 0.41
Exercise in 1982[4]					
None/Slight	156	105,260	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Moderate	285	264,391	0.71 (0.58–0.86)	0.74 (0.60–0.90)	0.83 (0.68–1.02)
Heavy	20	20,608	0.64 (0.40–1.02)	0.67 (0.42–1.07)	0.80 (0.50–1.28)
				p-trend = 0.003	*p*-trend = 0.08
Recreational activity MET-hr/week at age 40[4]					
None	64	57,878	0.91 (0.67–1.23)	0.93 (0.68–1.26)	0.92 (0.68–1.25)
0<–<7	119	97,393	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
7–<17.5	146	115,712	1.02 (0.80–1.30)	1.02 (0.80–1.30)	1.03 (0.81–1.32)
17.5–<31.5	78	74,574	0.84 (0.63–1.12)	0.83 (0.63–1.11)	0.81 (0.61–1.08)
31.5–<42	28	20,991	1.09 (0.73–1.65)	1.11 (0.73–1.68)	1.11 (0.73–1.68)
42+	25	22,236	0.92 (0.60–1.42)	0.94 (0.61–1.45)	0.96 (0.63–1.49)
				p-trend = 0.74	*p*-trend = 0.72
Long-term exercise[4,5]					
None/consistently low	142	90,185	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Low 1982, High 1992	14	15,075	0.58 (0.34–1.01)	0.58 (0.34–1.01)	0.65 (0.37–1.13)
High 1982, Low 1992	229	203,277	0.69 (0.56–0.86)	0.72 (0.58–0.89)	0.81 (0.65–1.00)
Consistently high	76	81,722	0.58 (0.44–0.76)	0.61 (0.46–0.80)	0.75 (0.56–0.99)

[1]Age-adjusted Hazard rate ratio and corresponding 95% confidence interval.–[2]Multivariate-adjusted RR and corresponding 95% CI adjusted for age, age at menarche, age at menopause, duration of OC use, parity, smoking, total caloric intake, personal history of diabetes and postmenopausal HT use.–[3]Multivariate-adjusted RR and corresponding 95% CI also adjusted for BMI.–[4]Numbers may not equal total due to missing information.–[5]Combination of exercise prospectively collected in 1982 and recreational physical activity at baseline 1992.

reational physical activity and endometrial cancer risk (RR = 1.01, 95% CI, 0.69–1.48 for >17.5 MET-hr/week *vs.* <7 MET-hr/week; trend $p = 0.51$), whereas risk of endometrial cancer was significantly lower in active women who were overweight or obese (BMI $\geq$ 25.0) than in inactive women (RR = 0.59, 95% CI, 0.42–0.83; trend $p = 0.003$) (Table III). We examined the associations while adjusting more finely for BMI and did not observe any appreciable differences in results (data not shown). Thus, in an effort to provide the most stable risk estimates, without compromising quality, we collapsed BMI categories. Results for overweight and obese women also did not differ appreciably and were therefore combined to provide more stable risk estimates. We also examined effect modification by BMI with both nonrecreational activity and sedentary behavior; however, did not observe any statistically significant interactions (data not shown). This was likely due to our limited power to examine associations in the highest levels of these exposures when stratifying by BMI. We found no suggestion of interactions between measures of physical activity or sedentary behavior and any of the other potential risk factors included in this analysis (data not shown).

Discussion

Results from this prospective study provide further support for a role of recent light and moderate physical activity (recreational and household) in lowering risk of endometrial cancer. Previous studies have reported a decrease in risk among the most physically active study subjects ranging from 20 to 90%, with a recent meta-analysis showing a pooled average of approximately 25% reduction in risk.[8] Our results are consistent with this pooled estimate for recreational physical activity. Additionally, our results agree with 4 of 5 previous studies that have shown associations between endometrial cancer and nonrecreational (daily life, household) activity[9,11,17,18] as well as sedentary behavior.[11,19]

There is strong biologic rationale to support the role of physical activity in lowering endometrial cancer risk. Exposure to unopposed estrogen is the major determinant of endometrial carcinogenesis,[2,31] and physical activity has been shown to decrease postmenopausal estrogen levels directly or indirectly through reducing peripheral fat stores, the major source of postmenopausal estrogen synthesis.[32–35] Hyperinsulinemia has also been implicated in endometrial carcinogenesis through several proposed mechanisms (reviewed in Ref. 2). Higher levels of insulin are associated with decreased levels of SHBG, resulting in increased levels of free estradiol.[36] Insulin may also act directly on endometrial tissue as a mitogenic growth factor, and may downregulate IGFBP-1 leading to a greater bioavailability of free IGF-1.[2] Independent of its effects on body mass, physical activity increases insulin sensitivity and decreases plasma insulin levels in postmenopausal women who engage in low to moderate levels of activity.[37]

Excess weight is a strong risk factor for endometrial cancer and is also associated with sedentary behavior. Therefore, we assessed whether the relationship between physical activity and endometrial cancer was confounded or modified by BMI. Adjustment for

TABLE III – HAZARD RATE RATIOS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR BASELINE RECREATIONAL PHYSICAL ACTIVITY AMONG NORMAL AND OVERWEIGHT/OBESE WOMEN IN RELATION TO ENDOMETRIAL CANCER, CPS-II NUTRITION COHORT, 1992–2001

	Baseline recreational activity MET-hr/week			
	None	>0–<7	7–<17.5	17.5+
BMI < 25.0				
Cases	6	52	58	53
Person-years	14,958	62,636	74,888	64,369
RR[1] (95% CI)	0.52 (0.22–1.21)	1.00 (ref.)	0.94 (0.64–1.36)	1.01 (0.69–1.48)
		trend $p = 0.51$		
BMI 25+				
Cases	37	118	99	43
Person-years	19,664	61,666	58,666	38,350
RR[1] (95% CI)	0.99 (0.68–1.43)	1.00 (ref.)	0.88 (0.67–1.15)	0.59 (0.42–0.83)
		trend $p = 0.003$		
		Heterogeneity of trends $p = 0.01$		

[1]Multivariate-adjusted RR and corresponding 95% CI adjusted for: age, age at menarche, age at menopause, duration of OC use, parity, smoking, total caloric intake, personal history of diabetes and postmenopausal HT use.

BMI in the multivariate analyses greatly attenuated the association between physical activity and endometrial cancer risk. However, a modest inverse association between physical activity and endometrial cancer remained even after adjustment for BMI. This suggests that physical activity has an effect on endometrial cancer that is not entirely mediated by BMI.

Furthermore, physical activity was strongly associated with lower risk of endometrial cancer only among overweight and obese women in our study. Our findings are consistent with 3[17,18,21] of 11 previous studies[9,11,12,15,17–23] that reported a greater risk reduction with regular physical activity among overweight or obese women compared to normal weight women. It is unclear whether the other studies observed interactions on less than a multiplicative scale, *i.e.* an additive scale, or were not adequately powered to detect an interaction based on data provided. Since physical activity, even in the absence of weight loss, significantly improves insulin sensitivity and has direct effects on bioavailable estrogen,[37] it is biologically plausible that overweight or obese women engaging in regular physical activity may experience a greater risk reduction compared to active, normal weight women.

Our study has several limitations. We have no information on the intensity with which individuals engage in each behavior thus increasing the likelihood of misclassifying true energy expenditure. While the physical activity questions we used have not been validated and are subject to misreporting, they are very similar to those used and validated in another prospective study.[38] Wolf *et al.* found strong correlations between activity reported on past-week activity recalls and 7-day diaries and that reported on the questionnaire (0.79 and 0.62, respectively).[38] Despite the limitations in our physical activity measures, these measures have also been associated with lower risk of breast and colon cancer in this cohort.[39,40] We had limited statistical power to examine higher intensity activities since most highly active women engaged in walking with the addition of modest amounts of the other 6 reportable activities.

Strengths of our study include the prospective design which eliminated the possibility of recall bias and our ability to control for potential confounding by known endometrial cancer risk factors. The relatively homogenous characteristics of women in our study reduced the likelihood of residual confounding by unknown factors even though it also reduced the range of the physical activity exposure variables.

In summary, our results add to the growing body of evidence that light and moderate levels of physical activity, including daily life activities like household chores, may reduce the risk of endometrial cancer, especially among overweight and obese women. Our study also suggests that in addition to its effects mediated through BMI, physical activity may have an independent effect on lowering risk of endometrial cancer possibly through directly suppressing estrogen or increasing insulin sensitivity. Future studies should further examine the association between light-intensity activities and endometrial cancer risk to strengthen public health recommendations in this regard.

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論文名	The role of body weight in the relationship between physical activity and endometrial cancer: results from a large cohort of US women
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		ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象の内訳	対象	一般健常者	空白		( )		コホート研究
	性別	女性	( )		( )		( )
	年齢	62.8(±6.0)歳			( )		前向き研究
	対象数	10000以上			( )		( )
調査の方法		質問紙	( )				
アウトカム	予 防	な し	な し	ガン予防	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表

TABLE II – HAZARD RATE RATIOS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR MEASURES OF PHYSICAL ACTIVITY AT VARIOUS POINTS IN TIME AND ENDOMETRIAL CANCER, CPS-II NUTRITION COHORT, 1992–2001

	Cases	p-years	RR[1] (95% CI)	RR[2] (95% CI)	RR[3] (95% CI)
Baseline recreational activity MET-hr/week					
None	43	34,622	0.92 (0.66–1.28)	0.93 (0.67–1.30)	0.84 (0.60–1.17)
0<–<7	170	124,302	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
7–<17.5	157	133,553	0.86 (0.69–1.07)	0.86 (0.70–1.07)	0.92 (0.74–1.14)
17.5–<31.5	72	75,456	0.70 (0.53–0.92)	0.70 (0.53–0.93)	0.80 (0.60–1.05)
31.5+	24	27,264	0.65 (0.42–1.00)	0.67 (0.44–1.03)	0.79 (0.52–1.22)
				p-trend = 0.007	p-trend = 0.18
Baseline nonrecreational activity MET-hr/week[4]					
None	11	5,473	1.45 (0.78–2.69)	1.44 (0.78–2.66)	1.31 (0.71–2.44)
>0–5.0	132	96,620	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>5.0–<10.0	110	93,290	0.87 (0.67–1.11)	0.87 (0.67–1.12)	0.91 (0.70–1.17)
10.0–<18.5	103	96,592	0.77 (0.60–1.00)	0.77 (0.60–1.00)	0.79 (0.61–1.02)
18.5+	106	99,250	0.78 (0.60–1.01)	0.79 (0.61–1.03)	0.83 (0.64–1.07)
				p-trend = 0.07	p-trend = 0.13
Baseline sitting[4] (hr/day)					
<3	195	184,173	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
3–5	203	165,561	1.13 (0.93–1.38)	1.13 (0.92–1.38)	1.02 (0.83–1.25)
6+	56	36,584	1.40 (1.04–1.89)	1.40 (1.03–1.89)	1.18 (0.87–1.59)
				p-trend = 0.05	p-trend = 0.41
Exercise in 1982[4]					
None/Slight	156	105,260	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Moderate	285	264,391	0.71 (0.58–0.86)	0.74 (0.60–0.90)	0.83 (0.68–1.02)
Heavy	20	20,608	0.64 (0.40–1.02)	0.67 (0.42–1.07)	0.80 (0.50–1.28)
				p-trend = 0.003	p-trend = 0.08
Recreational activity MET-hr/week at age 40[4]					
None	64	57,878	0.91 (0.67–1.23)	0.93 (0.68–1.26)	0.92 (0.68–1.25)
0<–<7	119	97,393	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
7–<17.5	146	115,712	1.02 (0.80–1.30)	1.02 (0.80–1.30)	1.03 (0.81–1.32)
17.5–<31.5	78	74,574	0.84 (0.63–1.12)	0.83 (0.63–1.11)	0.81 (0.61–1.08)
31.5–<42	28	20,991	1.09 (0.73–1.65)	1.11 (0.73–1.68)	1.11 (0.73–1.68)
42+	25	22,236	0.92 (0.60–1.42)	0.94 (0.61–1.45)	0.96 (0.63–1.49)
				p-trend = 0.74	p-trend = 0.72
Long-term exercise[4,5]					
None/consistently low	142	90,185	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Low 1982, High 1992	14	15,075	0.58 (0.34–1.01)	0.58 (0.34–1.01)	0.65 (0.37–1.13)
High 1982, Low 1992	229	203,277	0.69 (0.56–0.86)	0.72 (0.58–0.89)	0.81 (0.65–1.00)
Consistently high	76	81,722	0.58 (0.44–0.76)	0.61 (0.46–0.80)	0.75 (0.56–0.99)

[1]Age-adjusted Hazard rate ratio and corresponding 95% confidence interval.–[2]Multivariate-adjusted RR and corresponding 95% CI adjusted for age, age at menarche, age at menopause, duration of OC use, parity, smoking, total caloric intake, personal history of diabetes and postmenopausal HT use.–[3]Multivariate-adjusted RR and corresponding 95% CI also adjusted for BMI.–[4]Numbers may not equal total due to missing information.–[5]Combination of exercise prospectively collected in 1982 and recreational physical activity at baseline 1992.

図表掲載箇所	P1880, Table2
概 要 (800字まで)	本研究は、アメリカのCPS-II Nutrition Cohortに参加した閉経後女性42,672名を対象に11年間の追跡調査を行い、身体活動量と子宮内膜がん発症との関連を検討したものである。質問紙から、過去1年間の速歩、水泳、球技などの余暇時間身体活動、ガーデニング、掃除、修繕などの家事活動、テレビ視聴や座位などの不活動時間を尋ね、それぞれの活動をメッツ値に換算し身体活動量を算出した。余暇時間身体活動量が週当たり7メッツ時未満の集団と比較すると、活動量が増えるごとに子宮内膜がん発症リスクの減少傾向はあるものの、有意な差はみられなかった。家事活動も同様に、活動量と発症リスクに負の相関傾向がみられたが、有意ではなかった。不活動時間については、時間の延長とともに発症リスクの上昇傾向がみられたが、同様に有意ではなかった。研究開始時に運動頻度が低く、かつ、追跡調査期間中も頻度が低いと回答した集団と比較すると、研究開始時および追跡期間中継続して運動頻度の高かった集団で子宮内膜がん発症リスクの有意な低下がみられた(0.75(95%信頼区間:0.56-0.99))。また、肥満度の高い集団(BMI>=25)においては、週当たり17.5メッツ時以上の余暇時間身体活動を実施することで発症リスクを低減させることが明らかとなった(0.59(0.42-0.83))。
結 論 (200字まで)	閉経後の女性コホートにおいて、特に肥満傾向の集団では余暇時間身体活動の実施が子宮内膜がん発症リスクを低減させることが明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に使用された研究である。肥満と身体活動が子宮内膜がんの発症及ぼす相互作用につて検討した点に意義がある。

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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 ≥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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対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	女性	( )		( )		( )
年齢	62.7(±6.1)歳			( )		前向き研究
対象数	10000以上			( )		( )

調査の方法	質問紙	( )				
アウトカム 予 防	なし	なし	ガン予防	なし	( )	( )
アウトカム 維持・改善	なし	なし	なし	なし	( )	( )

図 表

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
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>0–<8	117/24,297	192,996	0.88	0.58, 1.32	0.87	0.58, 1.30
8–<17.5	89/14,597	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, 1.65	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	61/14,416	115,018	1.09	0.80, 1.49	1.08	0.79, 1.48
≥18.5	82/16,039	119,680	1.07	0.79, 1.46	1.07	0.79, 1.46
Missing	5/691	5,003	1.47	0.59, 3.63	1.49	0.57, 3.47
					p_{trend} = 0.56	
MET-hours/week at age 40 years						
None	39/8,659	69,062	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	0.69, 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} = 0.59	
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	25,356	0.89	0.50, 1.58	0.88	0.49, 1.55
Missing	3/738	5,900	0.81	0.25, 2.58	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.

図表掲載箇所	P713, Table2
概 要 (800字まで)	本研究は、アメリカのThe American Cancer Society Cancer Prevention Study II Nutrition Cohortに参加した閉経後女性59,695名を対象に9年間の追跡調査を行い、余暇時間身体活動量と不活動のどちらが卵巣がん発症リスクに影響を及ぼすかを検討したものである。余暇時間身体活動については、過去1年間で次の身体活動を週当たりどのくらい行ったか(ウォーキング、ジョギング、水泳、テニス、自転車、健康体操、ダンス)を尋ね、それぞれの活動に相当するメッツ値と時間積により、身体活動量をメッツ時/週で算出した。余暇時間外の身体活動については、過去1年間で次の身体活動を週当たりどのくらい行ったか(ガーデニング、きつい家事仕事、修繕作業、買い物)を尋ね、同様に身体活動量を算出した。不活動時間については、過去1年間で仕事時間を除き、1日当たりの平均座位時間(テレビ視聴、読書など)を尋ね、3時間/日未満、3-5時間、6時間/日以上の3群に分類した。1日当たりの座位時間が3時間未満の集団と比較すると、6時間以上で卵巣がん発症リスクが1.55(95%信頼区間:1.08-2.22)と有意に上昇した。余暇時間活動、余暇時間外活動では有意な関連はみられなかった。
結 論 (200字まで)	閉経後女性コホートにおいて、余暇時間身体活動は卵巣がん発症リスクとの有意な関連はみられなかったものの、不活動時間の延長が卵巣がん発症リスクを増加させることが明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。長い座位時間が高い卵巣がん発症と関係することを示し、特に座位時間が身体活動とは独立して、卵巣がん発症のリスクと関連することを実証した点に意義がある。

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Screen-Based Entertainment Time, All-Cause Mortality, and Cardiovascular Events

Population-Based Study With Ongoing Mortality and Hospital Events Follow-Up

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Objectives The aim of this study was to examine the independent relationships of television viewing or other screen-based entertainment ("screen time") with all-cause mortality and clinically confirmed cardiovascular disease (CVD) events. A secondary objective was to examine the extent to which metabolic (body mass index, high-density lipoprotein and total cholesterol) and inflammatory (C-reactive protein) markers mediate the relationship between screen time and CVD events.

Background Although some evidence suggests that prolonged sitting is linked to CVD risk factor development regardless of physical activity participation, studies with hard outcomes are scarce.

Methods A population sample of 4,512 (1,945 men) Scottish Health Survey 2003 respondents (≥35 years) were followed up to 2007 for all-cause mortality and CVD events (fatal and nonfatal combined). Main exposures were interviewer-assessed screen time (<2 h/day; 2 to <4 h/day; and ≥4 h/day) and moderate to vigorous intensity physical activity.

Results Two hundred fifteen CVD events and 325 any-cause deaths occurred during 19,364 follow-up person-years. The covariable (age, sex, ethnicity, obesity, smoking, social class, long-standing illness, marital status, diabetes, hypertension)-adjusted hazard ratio (HR) for all-cause mortality was 1.52 (95% confidence interval [CI]: 1.06 to 2.16) and for CVD events was 2.30 (95% CI: 1.33 to 3.96) for participants engaging in ≥4 h/day of screen time relative to <2 h/day. Adjusting for physical activity attenuated these associations only slightly (all-cause mortality: HR: 1.48, 95% CI: 1.04 to 2.13; CVD events: HR: 2.25, 95% CI: 1.30 to 3.89). Exclusion of participants with CVD events in the first 2 years of follow-up and previous cancer registrations did not change these results appreciably. Approximately 25% of the association between screen time and CVD events was explained collectively by C-reactive protein, body mass index, and high-density lipoprotein cholesterol.

Conclusions Recreational sitting, as reflected by television/screen viewing time, is related to raised mortality and CVD risk regardless of physical activity participation. Inflammatory and metabolic risk factors partly explain this relationship. (J Am Coll Cardiol 2011;57:292–9) © 2011 by the American College of Cardiology Foundation

There is indisputable evidence on the links between physical activity and risk for premature death (1). Some emerging published reports consistently suggest that excessive sedentary behavior (as characterized by those activities involving sitting) might be linked to increased risk for obesity (2,3), dyslipidemia (4), plasma glucose levels (5), and the metabolic syndrome (6) independently of moderate-to-vigorous physical activity participation. Television viewing and screen-based entertainment (screen time) in general seems to be the most important indicator of nonoccupational sitting behavior (7). Recent time-use surveys (8–10) indicate that, aside from sleeping, watching TV is the behavior that occupies the most time in the domestic setting.

If sitting or total sedentary time is established to be independently associated with cardiovascular disease (CVD), clinical and public health recommendations should explicitly address sitting in addition to physical activity; currently they do

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not (11). Because only a minority of adults in western populations participate regularly in sport and exercise activities (12,13), and those who do not take part in sports are more likely to develop CVD or die prematurely (14), it might be possible to reduce the risk of nonparticipants by restricting sitting time and increasing nonexercise activity (e.g., standing and ambulating) throughout the day (15). There is no conclusive evidence obtained from comparing the feasibility or long-term effectiveness of interventions designed to increase formal exercise versus decreasing sitting behavior during the day. However, the latter approach might be more promising in terms of long-term adherence, because it will involve more subtle lifestyle changes and fewer of the commonly cited barriers (16) for joining a sporting or lifestyle exercise program.

The primary aim of this study was to examine the relationships of leisure-time sitting behavior (indexed from screen time) with all-cause mortality and CVD events while taking multiple measures to address reverse causality. Because it is also important to understand the mechanisms through which sedentary behavior might influence cardiovascular risk, a secondary aim was to determine the extent to which several biomarkers explain these relationships.

Methods

Sample and outcomes. The 2003 Scottish Health Survey (SHS03) was a household-based survey that recruited a population sample with multistage, stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage (17). Ethical approval was granted by the Local Research Ethics Councils. Of eligible adults, 83% consented to take part in the survey. The SHS03 data were linked to the Scottish Information Division Database (ISD) patient-based database of hospital episodes (from 1981 onwards) and deaths up to December 2007. The linked data are of excellent quality—the ISD database has demonstrated 94% accuracy and 99% completeness when samples of computerized CVD records from the Scottish national database were compared with the original patient case notes. Information on deaths was ascertained from the General Registrar Office for Scotland. Classification of the underlying cause of death is based on information collected on the medical certificate of cause of death together with any additional information provided subsequently by the certifying doctor. All the relevant details regarding the ISD can be found at the ISD Scotland website. Diagnoses for CVD cause of death was recorded with the International Classification of Diseases-9 (codes 390-459) and -10 (codes I01-I99). An event was defined as CVD-related hospital episode (including myocardial infarction, coronary artery bypass, angioplasty, stroke, heart failure) or CVD-related death. The potentially eligible sample comprised 6,353 adults (≥35 years), of which 5,814 (91.5% of eligible) consented to their records being linked to records of mortality, hospital episodes, and cancer registration. Among these, 1,302 (22.4% of consenting) were lost to follow-up, leaving 4,512 respondents (1,964 male) who comprised the core sample for the present study (71.0% of eligible). We carried out comparisons between those who consented and those who did not consent to be followed up with likelihood ratios (categorical variables) or Student *t* tests (continuous variables). Compared with those who did not consent, those who consented were older; reported fewer moderate-to-vigorous physical activity and more screen time min/week; and more likely to be from nonmanual social class, white, not to be married, to have a body mass index (BMI) under 30 kg/m^2, to be current or former cigarette smokers, to have long-standing illness, to be inactive at work, to have been diagnosed with hypertension, and not to meet the physical activity recommendations. We also carried out comparisons between those 1,302 participants who were lost to follow-up and those 4,512 who were retained in the analyses. Those who were lost to follow-up were younger and reported more moderate-to-vigorous physical activity and less screen time min/week than those who were retained. They were also were more likely to be from nonmanual social class, to be single, to be current or ex-cigarette smokers, to be free from long-standing illness and doctor-diagnosed hypertension, and to meet the physical activity recommendations.

Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
CRP = C-reactive protein
CVD = cardiovascular disease
HDL = high-density lipoprotein
HR = hazard ratio

Analyses with cardiovascular events as the outcome excluded 340 respondents who had cardiovascular hospital episodes according to the linked patient-based database between 1981 and before baseline testing. To minimize the chances of reverse causality due to prodromal/undiagnosed disease, we repeated the analyses after excluding another 48 participants with cardiovascular events in the first 24 months of follow-up (CVD analysis). We also repeated the analysis after excluding the 295 participants who had cancer registrations before baseline.

Exposures, confounders, and potentially mediating variables. The main exposure was screen time. Two questions enquired about screen time on weekdays ("Thinking of weekdays, how much time on average day do you spend watching TV or another type of screen such as a computer, or video game? Please do not include any time spent in front of a screen while at school, college or work") and weekend days (with an equivalent question). Although there is no information on the reliability and criterion validity of the screen time questions, the previously reported (2) consistent direct correlations of screen time with waist circumference and BMI and the inverse correlation with physical activity support their convergent validity. Nonoccupational physical activity questions included frequency (days in the last 4 weeks) and duration (min/day) of heavy housework (e.g., scrubbing floors), heavy do-it-yourself/gardening (e.g., digging, building work), walking (14), and any leisure-time exercise (e.g., cycling, swimming, aerobics, calisthenics,

gym, dancing, football) (12). Occupational physical activity was assessed by asking respondents how physically active they are at work (very/fairly active, not very/not at all active). Their response was combined with information on their occupation with the Standard Occupational Classification 1990 (18) to classify work activity. The criterion validity of the physical activity questionnaire is supported by an accelerometry study on 106 British adults (19). Height, weight, socioeconomic status, health status, and other health behaviors were measured by trained interviewers with standard protocols (2,17). In a separate visit, trained nurses collected nonfasting blood samples with standard protocols and procedures that have been described previously in detail (14,20). Blood sample analytes used in the present analysis were C-reactive protein (CRP), high-density lipoprotein (HDL) cholesterol, and total cholesterol (17,21).

Variable handling and statistical analysis. Screen time was grouped as <2 h/day; ≥2 h/day <4 h/day; ≥4 h/day. The choice of 2 h/day as a cutoff for the lowest screen time group is consistent with recommendations for children (20,22) that make specific references to TV. The same cutoff has been used in publications similar to ours (23). The main confounding variable was nonoccupational moderate-to-vigorous physical activity, which was entered in the statistical models as min/day. Other covariables entered into the models were sex, age, BMI (<25, 25 to 30, >30 kg/m^2), social class (I, II, III nonmanual, III manual, IV/V nonmanual), doctor-diagnosed diabetes and hypertension, long-standing illness, marital status (single/never married, married, separated/divorced, and widowed), smoking (never, ex, current smoker), and occupational physical activity (inactive/light/moderate-to-vigorous).

For individuals who survived and remained CVD-free, data were censored to December 2007. The Cox proportional hazards model was used with months as the time scale to estimate the risk of death from any cause or the risk of CVD event by screen time level. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. Test for linear trend was obtained by entering the categorical variables as continuous parameters in the models. We applied Cox models that were adjusted for age and sex (Model 1), plus all covariables minus physical activity (Model 2), plus physical activity (Model 3). To account for the skewed distribution of physical activity, in an alternative analysis we re-ran the Cox models with physical activity as a categorical variable (no physical activity vs. some physical activity, <150 min/week vs. ≥150 min/week), but because results were not appreciably different, we only present the models with the continuous physical activity variables. To further address the issue of reverse causality, we repeated the Cox models after excluding CVD events occurring during the first year of follow-up and cancer registrations before baseline. In another analysis we excluded events in the first 2 years of follow-up and cancer registrations. In these analyses, we dichotomized the screen time variable to <2 and ≥2 h/day to preserve statistical power. For the same reason, we used the same dichotomous screen time variable when we stratified our analyses by sex, physical activity level (<150 min/week vs. ≥150 min/week; no physical activity/any physical activity), BMI level (<25 kg/m^2 vs. ≥25 kg/m^2), and smoking (noncurrent smoker vs. current smoker). To provide a direct comparison for the potential hazard of screen time and the potential benefit of physical activity, we ran analogous Cox models with physical activity as the main exposure with adjustments for: 1) age and sex; 2) plus nonscreen time covariables; 3) plus screen time. To enable direct comparisons, both screen time and physical activity were entered as continuous variables in this analysis.

To test the extent to which certain biological risk factors explained the association between sedentary time and cardiovascular events, we used a method similar to that used by us (21) and others (24). This method involved: 1) separately adding CRP, BMI, total cholesterol, and HDL cholesterol into a basic (sex-, age-, and physical activity-adjusted) Cox model; and 2) using the following formula to calculate proportion of CVD risk explained by each biological risk factor:

$$\frac{\text{HR basic model} - \text{HR adjusted}}{\text{HR basic model} - 1} \times 100$$

The CRP was log transformed to improve normality of distribution. All blood variables and BMI were included as continuous variables. Analyses were also run entering risk markers as categorical variables, although this did not appreciably alter the results. We used analysis of variance with Scheffe post hoc tests and chi-square tests to examine univariable relationships of the confounders or potential mediators with the exposure variables.

Analyses were performed with SPSS (version 13, SPSS, Inc., Chicago, Illinois), and all tests of statistical significance were based on 2-sided probability.

Results

A total of 325 any-cause deaths (153 in men) and 215 incident cardiovascular events (107 in men) occurred during 4.3 (±0.5) years of average follow-up and 19,364 person-years at risk in the core sample. Table 1 presents the descriptive characteristics of the core sample.

Cox models. Table 2 shows the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and CVD events. All-cause mortality risk increased with ≥4 h/day of screen time, and CVD event risk increased with ≥2 h/day of screen time. Adjusting for physical activity made very little difference in both types of analyses (Table 2). Excluding deaths or CVD events in the first year of follow-up and participants with previous cancer registration slightly weakened the associations (Table 3). Results were robust to the exclusion of cases with cancer registrations and CVD

Table 1 Descriptive Characteristics of Core Sample by Time Spent on TV Viewing and Other Screen-Based Entertainment

	TV Viewing and Other Screen-Based Entertainment			
	<2 h/day	≥2 and <4 h/day	≥4 h/day	p Value
n	771	2,441	1,300	
Mean age (SD)	55.7 (14.9)	57.2 (13.7)	60.4 (14.1)	<0.001
Sex (% male)	37.9	43.2	47.5	<0.001
Ethnicity (% white)*	96.9	98.4	98.5	0.034
Social class (% manual)*	58.4	65.6	76.0	<0.001
BMI (% >30 kg/m^2)*	18.2	23.6	29.2	<0.001
Marital status (% married/cohabiting)*	59.7	67.8	54.6	<0.001
Smoking status (% never smoked)*	49.7	41.5	32.5	<0.001
Long-standing illness (%)	47.5	51.5	66.5	<0.001
Doctor-diagnosed hypertension	27.3	31.1	39.9	<0.001
Doctor-diagnosed diabetes	3.5	5.2	9.6	<0.001
Mortality				
Died, any cause (%)	5.4	5.6	11.2	<0.001
CVD event, fatal (%)	1.2	2.4	4.9	<0.001
CVD event, nonfatal (%)	6.7	8.6	12.3	<0.001
Person-yrs	3,328	10,548	5,488	
Moderate-to-vigorous physical activity				
Mean (IQR), min/day	41.0 (57.2)	35.4 (49.3)	20.8 (5.7)	<0.001§
Occupational physical activity level, % inactive*	63.4	67.9	82.5	<0.001
Screen-based entertainment				
Median (IQR), min/day	67.3 (35.0)	173.6 (42.9)	381.3 (132.9)	n/a
Explanatory biological risk factors†				
Median CRP (IQR), mg/l ‡	1.3 (2.0)	1.7 (3.1)	2.4 (4.4)	<0.001§
Mean total cholesterol (SD), mmol/l	5.84 (1.09)	5.90 (1.12)	5.99 (1.17)	0.168
Mean HDL cholesterol (SD), mmol/l	1.61 (0.39)	1.54 (0.38)	1.45 (0.37)	<0.001
Mean BMI (SD), kg/m^2	27.0 (4.5)	28.0 (5.0)	28.4 (7.8)	<0.001

Scottish Health Survey 2003, participants 35 years of age and older who consented to their survey data, linked with mortality and hospital stay records. *Only one key category of the variable is shown; †n = 1,928 with valid values in all 4 listed biological variables; ‡C-reactive protein (CRP) was log transformed; §assessed with nonparametric test (Spearman rho) due to its skewed distribution.

BMI = body mass index; CVD = cardiovascular disease; HDL = high-density lipoprotein; IQR = interquartile range.

events in the first 2 years of follow-up (CVD events n = 116): the covariable-adjusted (minus physical activity) HR for those with ≥2 h/day was 1.94 (95% CI: 1.00 to 3.76); further adjustment for physical activity did not appreciably change this result (HR: 1.93, 95% CI: 0.99 to 3.75). When we repeated the main analyses with screen time entered as a continuous variable (min/day), results were similar in terms of direction and strength of the association with CVD events (age- and sex-adjusted HR: 1.0014; 95% CI: 1.0006 to 1.0022, p < 0.001; fully adjusted including physical

Table 2 HRs for All-Cause Mortality and CVD Events for Screen-Based Entertainment Groups* Excluding Previous CVD Hospital Stays

		HR (95% CI)		
	Cases/Events	Model 1†	Model 2‡	Model 3§
All-cause mortality				
<2 h/day	791/42	1.00	1.00	1.00
≥2–<4 h/day	2,492/138	1.13 (0.080–1.60)	1.12 (0.79–1.56)	1.14 (0.80–1.62)
≥4 h/day	1,311/146	1.77 (1.25–2.50)	1.52 (1.06–2.16)	1.48 (1.04–2.13)
Trend p value		<0.001	0.013	0.029
CVD events				
<2 h/day	745/18	1.00	1.00	1.00
≥2–<4 h/day	2,333/115	2.20 (1.30–3.71)	2.22 (1.32–3.77)	2.23 (1.31–3.80)
≥4 h/day	1,172/86	2.76 (1.62–7.70)	2.30 (1.33–3.96)	2.25 (1.30–3.89)
Trend p value		0.001	0.009	0.010

*Compared with the referent <2 h/day screen-based entertainment group. †Model 1 covariables: age, sex; ‡Model 2: plus body mass index, smoking, marital status, ethnicity, social class, long-standing illness, occupational physical activity, doctor-diagnosed diabetes and hypertension; §Model 3: plus moderate-to-vigorous physical activity.

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.